Dermatology in Public Health Environments

A Comprehensive Textbook

Renan Rangel Bonamigo
Sergio Ivan Torres Dornelles

Editors

Springer

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Foreword

The invitation to present *Dermatology in Public Health Environments* is certainly among the most honorable in the almost 30 years I devoted to public health dermatology. Having known the organizers for long time, I am sure that, in addition to the search for updated knowledge, high scientific rigor, and careful selection of experienced practicing professionals for writing the chapters, it was a work of love for my fellow beings.

Dermatologic conditions are among the most frequent reasons for the seeking health care. They produce suffering, low quality of life, and overburden of services. They also generate direct and indirect high costs. Access to health services is difficult in middle- and low-income countries, but even in industrialized countries access is far from ideal. A less than optimal approach, which is common especially in primary care services, increases costs and complications.

I am certain that this fully illustrated textbook will be very useful for doctors, nurses, psychologists, and physiotherapists, whether they are in training or full professional activity. The multidisciplinary approach reveals the concern for comprehensive care in outpatient clinics, aiming at improving care and reducing costs. Public health concepts that are not always available to clinically active professionals are innovatively presented in part I. Parts II to VI include in-depth information on different dermatologic conditions, and part VII on systemic diseases with frequent dermatologic manifestations. Practical and helpful is the section on signs and symptoms (part IX). Also innovative is part VIII, which covers emerging issues related with environmental problems and those arising from various human activities.

I reiterate my confidence in the importance of *Dermatology in Public Health Environments* (*Bonamigo RR and Dornelles SIT – editors*), and I am sure that both professionals and patients will be grateful for this great endeavor carried out with excellence.

Mauro Cunha Ramos, MSc, PhD, Dermatologist

"If you can look, see. If you can see, repair"

José Saramago (book: Ensaio Sobre a Cegueira)

Preface by Renan Rangel Bonamigo

Publishing a Dermatology book with an emphasis on public health has a great meaning: it demonstrates that the health of a population is intrinsically related to the social conditions into which it is inserted.

Dermatology is a specialty of daily human suffering, and we consider that each professional involved in care can act to minimize this. Furthermore, it is essential that managers of health systems acquire knowledge of the epidemiologic characteristics of the main dermatologic diseases.

We hope that this book will be useful to students and professionals who are interested in understanding patients with a dermatologic problem and, within academic, scientific, and ethical high precepts, seek to help; and that it is also useful for understanding the multiple relationships that exist between public health and the environment, socioeconomic conditions, and priorities determined by governments and nations.

Acknowledgements

Dedication

This book is for all those who dedicate their professional lives to Public Health and, to represent them, I dedicate it especially to Yuçara T. Rangel Bonamigo, a Brazilian nurse who worked in Public Health for many years, as an actual humanistic reference.

Porto Alegre, Brazil   Renan Rangel Bonamigo, MD, PhD

Preface by Sergio Ivan Torres Dornelles

Public health are words that elicit the art and science of preventing disease, prolonging life, enabling health and physical and mental efficiency through the community's organized endeavor. This book results from one idea and the opportunity to make available to health care teams an enriching material to help increase the knowledge of dermatologic diseases affecting the population, by aiming higher than the characteristics that help diagnosis, prevention, and treatment. Some chapters in this book address a series of appropriate measures to develop a social structure that possibly provides all social individuals with necessary health care. This team work by Springer, the editors, and authors certifies health accomplishments that enable an outstanding level of knowledge in Dermatology.

It is already known that the scientific research is traditionally based on reliability. In order to keep such virtue intact and unsuspicious in the scientific environment, a reliable work has to allow for the validation of the reported results by accepting what is made known by the specialized literature as a source of new knowledge. Therefore, the so-called scientific community has to follow behavioral standards not only in the research itself but also in the disclosure of the acquired information and knowledge. These standards were strictly followed in this book because the invited authors have undisputedly followed them. For this reason we are extremely grateful for their extensive contribution to this project and commitment to science.

As editors we expect this book to provide easy access to knowledge for all professionals related to public health, and the provision of improved health and comfort to the population.

Acknowledgements

Life provides many moments to say "thank you". This is one of these moments. Teachers, colleagues, students, patients, they all had significantly motivated us to write this book and that is why we must thank them all. We now say "Thank you" and want you to feel honored.

But I send my special thanks to my family, always central when opportunities must be sought. Therefore, the major foundation which guided my steps toward this goal is my family. My parents provided me a wonderful experience during a first phase; three extremely significant people were the highlights during the second phase, my wife Susana, and my sons Lúcio and Marcel. Thank you so much!

Dedication

For this work to have a long reach in time we must dedicate it to those who somehow helped us to write it. So this book is for all my colleagues from the Outpatient Clinic of Sanitary Dermatology (Ambulatório de Dermatologia Sanitária), where I had worked for three decades, a place that taught me how to give comfort to the less favored. But I have to mention that it was a sought after and cultivated idea which enabled us to collect all of this information, whose progenitor was Professor Renan Rangel Bonamigo, well known for his scientific capacity and ethics. To Prof. Bonamigo, the main editor of this book and a scientific partner for over a decade, we should give full credit.

Another name has to be mentioned, that of Professor Roberto Lopes Gervini, since he was one of my most outstanding masters to whom I owe the most considerate thanks in the fields of science and life.

There is also room to honor all patients who trusted us with their faith and hope in our procedures, people who gave us the opportunity to learn all those details that do not belong in the medical literature.

Porto Alegre, Brazil   Sergio Ivan Torres Dornelles, MD, MSc

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Part I

Dermatology in Public Health

Concepts of Relevants Diseases in Public Health

João Luiz Bastos, Rodrigo Pereira Duquia,
and Jeovany Martínez-Mesa

Key Points Summary

- A public health approach to health and disease emphasizes health problems that are frequent, produce severe impacts on individuals/societies, and are amenable to change
- "Magnitude" refers to the frequency of health problems in the context of populations or some of their specific segments
- The impact of health problems on individuals and societies is frequently known as "transcendence"
- The extent to which knowledge and resources (be they human, material, financial, etc.) are available to tackle health problems corresponds to "vulnerability"

- Taken together, magnitude, transcendence, and vulnerability should be used to build a list of public health priorities, along with other relevant criteria
- Defining public health problems according to these and other concepts is key to offering high-quality care to all patients

Introduction

A public health approach to disease processes and health issues is often seen as fundamentally important whenever health policy development or health service planning is among the main activities to be carried out in the context of any health care system. However, such an approach is not commonly regarded as of utmost importance when clinical care is to be provided to patients or individuals in need. In fact, the clinical and population perspectives to health and disease are often taught in medical schools by distinct faculties of physicians or surgeons whose scopes of action do not seem to show a high degree of overlap. The end result is that these perspectives seem to be disconnected from each other for the majority of health professionals, even though they are complementary and, if mastered, greatly contribute to the provision of quality care to all health care users.

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Our primary goal in this chapter is to give salience to the intersections between the population and clinical perspectives, taking the concept of "public health problem" as a point of departure. By giving meaning to the conceptions of public health and epidemiology, we aim to present a set of technical criteria on which to base the definition of priorities in the health field: "magnitude," "transcendence," and "vulnerability." While we recognize that these are not exhaustive criteria on their own—that is, social, political, economic, and historical concerns should also be taken into account in the process of setting priorities—we do believe that they have sound potential to reconcile population and clinical perspectives, and to help bring the patient (as opposed to mere pathologic entities) back to the center of clinical care.

The chapter goes on to discuss causes of health and disease in populations and individuals, drawing from widely known publications and authors in the field of public health. An underlying assumption is that what causes diseases in population groups is different from what causes diseases in individuals. Such a distinction is needed, because the extent to which a health issue may be tackled by population or individual measures also helps to define a public health problem. Next, some dermatologic problems are presented and discussed in light of the aforementioned criteria in order to clarify that some health problems may be important from a population perspective, while also being clinically less serious (i.e., easily treated). Thus, both clinical and population approaches are depicted as complementary, even though they may not come to the same conclusions or point to similar needs when planning or effectively providing care to patients.

The text that follows is divided into four distinct subsections. The first, "Defining Priorities," reviews the following subjects: public health, epidemiology, public health problems, and causes of health/disease in populations and individuals. A subsection named "Practical Applications" brings examples of disease processes and health conditions that illustrate the application of the population and clinical perspectives; a list of terms or jargon is included under the heading "Glossary." Finally, interested readers are presented with three supplementary bibliographic references that offer additional thoughts and opportunity for further learning.

Defining Priorities

Public health has been defined in multiple ways in the past 100 years. It is mostly concerned with the application of knowledge to the organization of health care systems and health care services, as well as to factors that drive population patterns of health to control disease occurrence through continued surveillance and governmental interventions. One of the most famous definitions of public health dates back to the 1920s and was set forth by Charles-Edward Amory Winslow, a North American bacteriologist, public health expert, and professor at Yale University.

According to Winslow [1], "public health is the science and the art of preventing disease, prolonging life, and promoting physical health and efficiency through organized community efforts for the sanitation of the environment, the control of community infections, the education of the individual in principles of personal hygiene, the organization of medical and nursing service for the early diagnosis and preventive treatment of disease, and the development of the social machinery which will ensure to every individual in the community a standard of living adequate for the maintenance of health."

On the other hand, epidemiology is often regarded as a scientific discipline whose primary aim is to help public health achieve its own goals. Whether epidemiology has lost momentum in serving public health is a matter of controversy, and interested readers are referred to two specific publications for further discussions on this topic [2, 3]. Nevertheless, epidemiology is thought to be the cornerstone of public health, literally meaning "the study of what is upon the people," given that its etymology derives from the three Greek word roots "epi" (upon or among, in English), "demos" (people or population), and "logos" (study or scrutiny), clearly suggesting that epidemiology encompasses a population-based approach, not an individual one.

According to Gordis [4], a renowned North American epidemiologist, epidemiology "is the study of how disease is distributed in populations and the factors that influence or determine this distribution." Other definitions of epidemiology exist elsewhere [5, 6].

Indeed, we argue that most public health activists and epidemiologists would easily agree with our view that epidemiology is about frequency, distribution, and causes of health problems in a given population. By frequency, we mean the extent to which a specific population segment is affected by a certain health condition. For example, if 20 out of 1,000 city residents have diabetes, the frequency of this health condition would equal to $^{20}/_{1,000}$ or 2.0%. While the overall frequency of diabetes would be 2.0%, some groups within this population could present higher rates of such a chronic condition. Suppose that there were 600 women in this city and that 15 of them had diabetes; the frequency of diabetes among women would then amount to 2.5% ($^{15}/_{600}$), whereas the frequency of diabetes among men would equal to $^{5}/_{400}$ or 1.3%. When we compare the frequency of diabetes among different subgroups, we are, in fact, studying its distribution within the same population. Similarly, when we study factors that potentially underlie or are responsible for the frequency of diabetes, as well as its (often unequal) distribution in relation to any other social characteristic (e.g., gender), we are investigating the causes or determinants of the health problem in question.

Hence, it should be clear to the reader that what public health and epidemiology have in common is that both aim at addressing health problems in the context of populations: they either base their actions on "community efforts," as Winslow accurately acknowledged, or take "population" as the reference to study health profiles, following Gordis's conceptualization. However, not all health problems are accorded the same level of priority, and therefore do not warrant similar efforts toward their control, treatment, and/or prevention. When it comes to prioritizing health issues, the concept of "public health problem" becomes particularly relevant, and it is to this concept that we now turn.

What becomes a priority and is effectively addressed in the public health field is dependent upon several factors and their complex interrelationships. Of note, political, social, economic, and historical concerns play an important part in this process, and should never be thought of as irrelevant criteria upon which a list of the most important diseases is built. For instance, the concept of "neglected tropical diseases" was primarily coined to increase public awareness of a group of infectious diseases that are frequent in low-income populations in poor regions of the Americas, Asia, and Africa, but do not receive adequate treatment and sufficient research funding [7], i.e., they are not prioritized. Paradoxically, these are diseases for which reliable and efficient public health and individual measures are usually available, but which lack timely and adequate treatment or prevention due, in part, to a widespread disregard for the developing world on the part of powerful countries and international/national health agencies. In other words, neglected tropical diseases technically fit the criteria of a public health problem (whose concept is discussed in detail below), even though political, economic, and power relations among and within countries contribute to their long-standing persistence in the poorest and most vulnerable populations of the world.

What, then, should we take into consideration to classify a health condition as a public health problem? As argued in the previous paragraph, this question is far from settled, although we believe that the three following concepts are particularly useful in setting public health agendas and defining public health priorities. "Magnitude," which is commonly referred to by scholars in the public health field, pertains to the frequency of health problems in populations and their subgroups. According to this concept, the higher the frequency of a health condition, the higher the likelihood that it will be classified as a public health problem. Hypertension, for instance, is a widespread disease whose prevalence rates reach up to 40–50% in many populations worldwide. In contrast, the frequency of all types of cancer tends to be very low, especially in the general population, and not among patients admitted to

specialized oncology services. Therefore, if we considered only magnitude, we would conclude that hypertension is a public health problem, while all types of cancer are not. Nevertheless, "high magnitude" is not a mandatory attribute in classifying a health condition as a public health problem. An interesting example is the recent microcephaly epidemic associated with Zika virus infection described in Brazil and some other countries [8]. In absolute numbers, microcephaly cases attributed to Zika infection are perhaps insignificant, but ethically unacceptable. This example leads us to the discussion of a second criterion to define a public health problem: "transcendence."

Along with magnitude, "transcendence" must also be a criterion on which to build a list of public health priorities. Transcendence includes the impact of each health condition on individuals and societies as a whole. In the previous example of microcephaly and Zika virus infection, the impact of this condition on individuals, families, and the whole society explains why it could be considered a public health problem. In addition, take, for example, the case of dental caries. As well as causing pain, discomfort, and negatively influencing social interactions, dental caries is associated with absence from work and school, in addition to posing a great burden on dental health services because of treatment demands. Cancers are also burdensome, in that the quality of life is severely diminished and the associated costs of treatment are expressively high. Following this criterion, microcephaly, cancers, and dental caries would be public health problems, whereas mild health conditions with low impact on individuals/societies, such as sunburn, would not.

The third concept commonly used to define a public health problem is "vulnerability." Such a term is somewhat misleading to most readers, because vulnerability is more often than not attributed to individuals or specific population groups subjected to processes of marginalization and social exclusion. In this chapter, however, vulnerability refers to the existence of knowledge and availability of resources to efficiently tackle a specific health issue: literally, vulnerability is the extent to which a health condition is

"vulnerable" to changes through the application of existing knowledge and available resources. This means that only those problems for which effective measures of control, treatment, or prevention exist should be prioritized in terms of public health. Returning to the topic of microcephaly and Zika virus infection, the control of the vector, the *Aedes aegypti* mosquito, is key to combating disease transmission. However, this would only be achieved through the implementation of strategies at multiple levels: governments, communities, and individuals should all be engaged in actions to reduce mosquito breeding and disease transmission, including measures related to improved sanitation, early detection of cases, and adequate treatment of affected mothers and newborns. Another simple example is iron deficiency, which is controllable through community and individual actions based on the available knowledge and resources in most societies. Thus, according to the concept of vulnerability, iron deficiency and Zika virus infection should be regarded as public health problems.

Rothstein [9] contends that any health condition should be treated as a public health problem "when government action is more efficient or more likely to produce an effective intervention," as compared to individual measures, to address the problem. The distinction between problems that may be dealt with at the governmental/population level and those issues that are amenable to individual action brings us to one final clarification: causes of health and disease in populations are different from causes of health and disease in individuals.

As Rose [10] rightfully pointed out in 1985, the potential causes of diseases among individual cases will likely differ from the causes of diseases among populations. To fully understand this idea, let us consider a brief example. Suppose an epidemiologist carries out an investigation to ascertain whether fluoridation of public water supplies is associated with fewer dental caries lesions in children and adolescents. If the whole population under study is homogeneously exposed to water fluoridation, the investigator will not be able to demonstrate that caries levels vary according to access to fluoridated water, i.e.,

regardless of varying caries levels among groups of children and adolescents, the entire population is exposed to fluoridated water. Rather, the study of this specific population will easily point out that dental caries may, in fact, be linked to individual characteristics (sugar consumption, tooth brushing, use of dental floss, etc.) owing to the fact that these health-related behaviors vary a lot from individual to individual within the population. However, if the same investigator decides to compare this highly exposed population with another one, whose levels of fluoride exposure are lower, fluoridation of drinking water could be identified as a protective factor for dental caries. Therefore, depending on the groups being compared and the level of analysis (populations or individuals), investigators may identify different sets of causes for sick individuals or sick populations. In the case under consideration, sugar consumption, tooth brushing, and use of dental floss would be individual determinants of caries. On the other hand, fluoridation of water supplies would be a potential cause of dental caries according to a population perspective. If water fluoridation happens to be more effective in addressing dental caries, this health condition should be considered a public health problem.

As we finish this subsection we could argue that, broadly speaking, a public health problem is any health condition that presents magnitude, transcendence, and vulnerability; yet we could also add that public health problems are those which are more likely to change in response to population/governmental measures. It is important to note, however, that population/governmental measures will most likely be based on scientific knowledge of what causes diseases in populations rather than in individuals (e.g., a public health measure to prevent dental caries would focus on water fluoridation rather than on individual behaviors). There are exceptions to these criteria, of course, and other factors may play an important role in setting priorities. Nevertheless, we believe that the aforementioned criteria are crucial to setting priorities, because they bring people's lives and societal impacts to the fore, while not restricting public health problems to those whose expressions are fundamen-

tally biological, physiological, biochemical, or organic. In fact, our conceptualization of public health problems may include not only health states, diseases, and their biological expressions, but also their population determinants or related processes. According to this definition, lack of sanitation (which has profound health impacts) would also fit the criteria of a public health problem, and why shouldn't it?

Practical Applications

Several diseases or health states/processes in Dermatology could be deemed public health problems. Such health conditions could be ranked from those highly lethal (e.g., cutaneous melanoma) to those with mild clinical expression (e.g., capitis pediculosis, which is frequently associated with school absenteeism in children and adolescents and secondary infection). One of the most significant and stigmatizing dermatological diseases, however, is hanseniasis, which has been a public health problem for decades or even centuries in Brazil and worldwide.

Even though hanseniasis is a treatable infectious disease, it is still highly prevalent in many populations, especially those in developing countries [7]. Hanseniasis also potentially produces negative impacts on affected individuals, including granulomas of the nerves, respiratory tract, skin, and eyes. These granulomas may result in loss of sensation and eventual limb amputations. Dermatologists are extensively trained to diagnose and treat affected individuals. Nevertheless, whenever dermatologists face a public health problem, such as hanseniasis, the clinical approach to the case should be combined with the population-based approach to the problem, as we argue above. In these cases, the reasons that turn the disease in question into a public health problem must be discussed and considered in the course of treatment and development of strategies to face it from an individual and community perspective.

We believe that medical training which combines population and clinical perspectives to address health issues is on the horizon. Once this

is achieved, we shall successfully counteract important and persistent problems in many countries, especially those that remain inexplicably high in the poorest populations of the world.

Glossary

- Causes (of diseases or health states/processes): any factor, condition, or process that is responsible for changes or specific states in a specific health outcome
- Distribution (of diseases or health states/processes): frequency of a health condition according to personal, spatial, and/or temporal characteristics
- Epidemiology: study of disease frequency, disease distribution, and the causes that determine both disease frequency and disease distribution in human populations
- Frequency (of diseases or health states/processes): number of affected individuals relative to a specific population or group
- Magnitude: extent to which a given health condition is frequent in a given population
- Prevalence: refers to a simple mathematical calculation whereby the number of affected individuals is divided by the total population in question
- Public health problem: any health condition showing magnitude, transcendence, and vulnerability. It is important to note that, according to this chapter, other criteria are commonly used to define public health problems, including social, historical, economic, and political concerns
- Public health: "[…] the science and the art of preventing disease, prolonging life, and promoting physical health and efficiency through organized community efforts for the sanitation of the environment, the control of community infections, the education of the individual in principles of personal hygiene, the organization of medical and nursing service for the early diagnosis and preventive treatment of disease, and the development of the social machinery which will ensure to every individual in the community a standard of living adequate for the maintenance of health" [1]
- Transcendence: extent to which a health condition produces expressive negative impacts on individuals and societies
- Vulnerability: availability of knowledge and resources to counteract any health issue

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Suggested Literature

As a resource for further learning, we recommend the following bibliographic references to interested readers:

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International Public Health Strategies in Dermatology

2

Antonio Carlos Gerbase, Gabriel Roman, and Charifa Zemouri

Introduction

Structured strategies to tackle skin diseases and related infections (e.g. sexually transmitted infections) are necessary to provide a framework and direct actions against their burden. Usually this is not perceived at the clinical care level, the curative branch of the strategies where most resources are used. However, for professionals working at ministries of health and other leading institutions, and who are responsible for a comprehensive response, an organized strategic approach is fundamental. On the other hand, health professionals on the front line must understand the general issues of the strategic interventions in order to understand their role and strengthen the effectiveness of their actions.

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Strategies to treat skin diseases and related infection at an international level give directions to national strategies, which encompass not only provision of care and preventive measures but also interventions dealing with structural, environmental, cultural, and financial issues.

The WHO is the health agency of the United Nations system [1]. At an international level the WHO is the leading organization that, reacting to the global health situation and to regional and country requests, develops, updates, advocates, and disseminates international public health strategies and, subsequently, the norms, standards, and guidelines needed for their implementation. Established in 1948, it was until the end of the 1980s the only institution leading international health strategies on a global level. During the past decades other international foundations (e.g. Gates Foundation) and bilateral national agencies (from countries such as Germany, Sweden, United States, and United Kingdom) increased their role in international public health strategic interventions and frequently directly channeled resources to countries (e.g. PEPFAR). Nonetheless, the WHO is the only international public health institution that is accountable and responds to virtually all countries. Moreover, to improve the way strategies are conducted and

norms are set, the use of standard procedures has been developed in the past decade, including the use of the GRADE system for guideline development [2].

International strategies are developed by the WHO secretariat in close collaboration with the scientific community and member states. The duration of a typical WHO global strategy ranges from 5 to 10 years, although shorter or longer examples exist. The first global strategy in the modern use of the term was the Global Strategy on AIDS, developed by the Global Program on AIDS in 1991. Once a global strategy is formulated, member countries evaluate its implementation and efforts are made to measure its impact. When the new strategy is developed a consultation process is established, the drafts are widely circulated, regional and global meetings are conducted, and, finally, the strategy is presented for approval by the World Health Assembly (WHA), the main governing body of the WHO [3]. Countries approve and are committed to its implementation.

Once the strategies are approved by the WHA, specific guidelines are needed to support their implementation. The process to develop WHO guidelines follows the GRADE system, whose main characteristics are prioritization of problems; establishment of panels, developed from questions; systematic review of evidence; evidence summary; evaluation of outcomes; overall quality of evidence; evaluation of benefits/harms; strength of recommendation and implementation and evaluation of the guidelines; strict evaluation of evidence; participation of final consumers; and evaluation of quality. The guidelines using the GRADE method are strictly based on the available scientific evidence [2].

This chapter reviews the main WHO strategies related to skin diseases and related infections whose prevalence, incidence, and significant population burden permit them to be considered of public health importance.

State of the Art

WHO Strategies Related to Dermatology

Sexually Transmitted Infections

Key Point Summary
- The 2016–2021 strategy plan to end STI epidemics as a major public health concern targets the 90:90:90 reduction of the global STI prevalence and national human papillomavirus vaccine coverage.
- Standardized protocols and guidance that are people centered are needed to reach the targets as defined during the 69th WHA.
- Interventions are mainly focused on prevention, management of asymptomatic patients, reaching sex partners and treatment, access to STI services of adequate quality, reduce vulnerability and risks, and meet the needs of the general population with appropriate services.

Rationale

STIs result in a high burden of morbidity, mortality, quality of life, sexual and reproductive health, and newborn and child health. STIs facilitate the sexual transmission of HIV and increase the risk of some cancers through cellular changes. It is estimated that 357 million new cases of curable STIs (Fig. 2.1), *Neisseria gonorrhea*, *Treponema pallidum*, *Trichomonas vaginalis*, and *Chlamydia trachomatis*, occur every year among people aged 15–49 years. The prevalence of some viral STIs is similarly high as a result of herpes simplex type 2 virus (HSV-2) and HPV. This chapter focuses primarily on three infections, *N. gonorrhea*, *T. pallidum*, and HPV, which require immediate action for their control (see Boxes 2.1, 2.3, and 2.4).
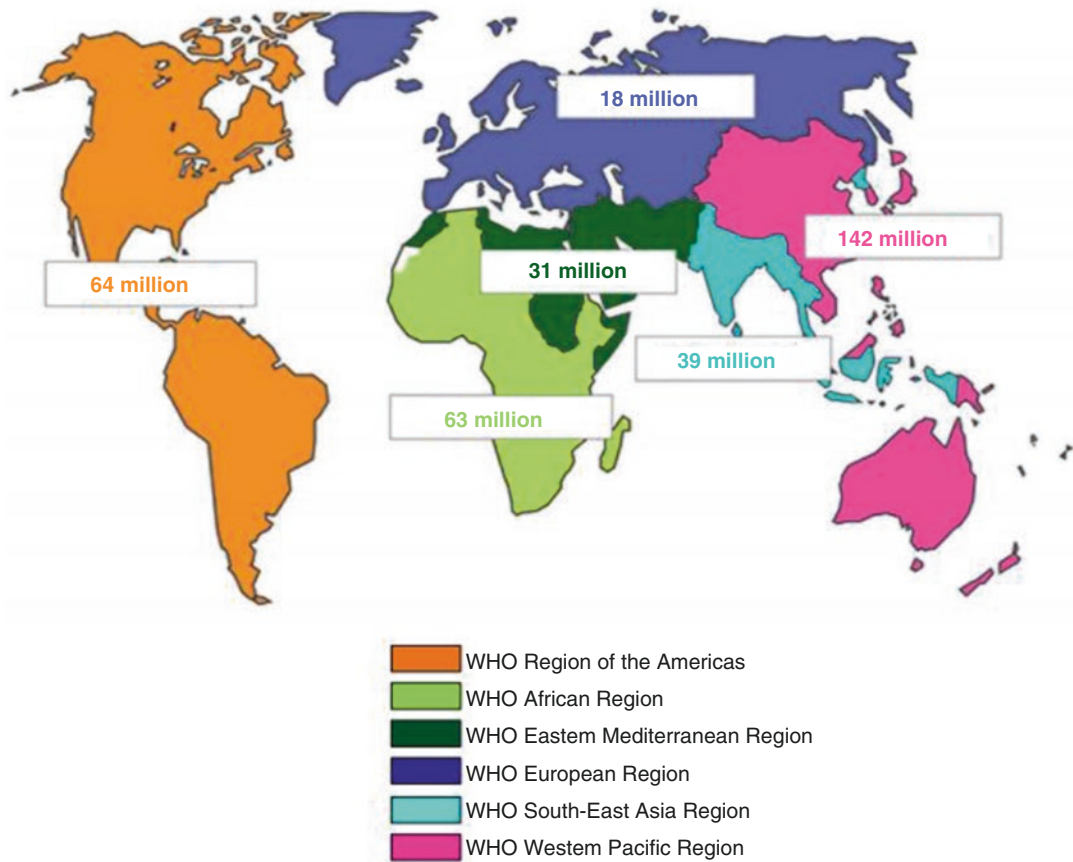
Fig. 2.1 New cases of curable STIs: annual estimate

Targets

The WHO developed a global strategy plan for 2016–2021 on STIs, responding to requests by member states [4]. The goal is to end STI epidemics as major public health concerns. The WHO's vision is to have zero new infections, zero STI-related complications and deaths, and zero discrimination and a world with free and easy access to STI prevention and treatment services, resulting in individuals being able to live long and healthy lives. A 90:90:90 target for 2030 is set up to reach 90% reduction of *T. pallidum* (syphilis) incidence globally, 90%

global reduction in *N. gonorrhea*, and sustainment of 90% national coverage of HPV vaccination in national immunization programs. Furthermore, the WHO has set up milestones for this strategy by 2020 (see Box 2.1).

For syphilis, there is a separate strategy and target. Syphilis in pregnancy leads to more than 300,000 fetal and neonatal deaths each year with 215,000 infants at increased risk for early death. The new strategy has set up a goal of 50 or fewer cases of congenital syphilis per 100,000 live births in 80% of the countries. To eliminate mother-to-child transmission, all pregnant women should be screened for syphilis and HIV simultaneously.

Strategies

To reach the targets there is a need to improve universal health coverage with improved quality health interventions and services, reduced costs, and financial protection for those in need of the services (see Fig. 2.2). The public health approach should focus on a standardized protocol and guidance, people-centered services, focus on equity, community participation, involvement of affected individuals, ensuring free or affordable services, and focus on population-based national plans. The first strategic step is for countries to acquire knowledge of their STI epidemic and to implement a tailored response; therefore, they need strategic information for advocacy and investments. Next, understanding the epidemics includes knowing where, how, and among whom new infections occur and identifying factors to facilitate access to appropriate services. Finally, national STI surveillance is needed to monitor infections among the populations and improve the strategies and interventions.

All persons should receive STI services they require, which should be of adequate quality. Countries should promote an enabling environment which includes policies and laws that promote human rights and gender equality. They should also reduce vulnerability and risk, and meet the needs of the general population with appropriate services. Specifically men and boys should be addressed, since they have often been overlooked in STI control. Countries should therefore engage and link with communities and partners, and strengthen the health systems to ensure access to quality vaccines, diagnostics, medicines, and other commodities. To achieve this goal, persons should receive the STI services they need without experiencing financial hardship. Innovative financing and new funding approaches, financial risk protection, reduced prices and costs, and improved efficiency strategies should be implemented.

Interventions

People should receive the full range of STI services they require. Therefore, countries need to define a set of core interventions. The following intervention areas should be covered:

- Prevent STI transmission and acquisition
- Achieve early diagnosis of STI and linkage to treatment
- Manage asymptomatic patients
- Reach sex partners and offer them treatment
- Maximum impact interventions include elimination of mother-to-child transmission of syphilis and HIV; HPV and hepatitis B virus vaccination; control the spread of antimicrobial resistance of gonococcals
- Ensure quality of care by strengthening prevention, diagnosis, treatment, and care; integrated services and programs; quality assurance and improvement of programs

The main intervention is to prevent STI transmission and acquisition. Countries need innovation for acceleration by optimizing STI prevention, diagnostics, medication, and treatment regimens but also by using existing tools more efficiently and adapting them for different populations, settings, or purposes. The current intervention recommendations for STIs are summarized in Boxes 2.2 and 2.3.

Box 2.1 Milestones for 2020

- 70% of countries have STI surveillance system in place
- 70% of countries screen at least 95% of pregnant women for HIV and/or syphilis
- 70% of key population for HIV have access to a full range of services relevant to STI and HIV, including condoms
- 70% of countries provide STI services
- 70% of countries deliver HPV vaccines
- 90% national coverage of HPV vaccines
- 70% of countries report on AMR in *N. gonorrhoeae*

Vision: Zero new infections, zero sexually transmitted infection-related complications and deaths, and zero discrimination in a world where everybody has free and easy access to sexually transmitted infection prevention and treatment services, resulting in people able to live long and healthy lives.

Goal: Ending sexually transmitted infection epidemics as major public health concerns.

2030 Targets:
90% reduction of *T.* pallidum incidence globally (2018 global baseline).
90% reduction in *N.* gonorrhoea incidence globally (2018 global baseline).
≤ 50 cases of congenital syphilis per 100 000 live births in 80% of countries
Sustain 90% national converge and at least 80% in every district (or equivalent administrative unit) in countries with the human papillomavirus vaccine in their national immunization programme.

Frameworks for action: Universal health coverage, the continuum of services, and a public health approach.

Monitoring and Evaluation

The three dimensions of UHC

STRATEGIC DIRECTION 1

Information for focused action

The "who" and "where"

STRATEGIC DIRECTION 2

Interventions for impact

The "what"

STRATEGIC DIRECTION 3

Delivering for equity

The "how"

STRATEGIC DIRECTION 4

Financing for sustainability

The financing

STRATEGIC DIRECTION 5

Innovation for acceleration

The future

STRATEGY IMPLEMENTATION:
Leadership, Partnership, Accountability, Monitoring & Evaluation

COUNTRY ACTION

Country Partner Action

WHO ACTION HQ, REGIONS AND COUNTRIES

Global Partner Action

Fig. 2.2 Outline of the draft global health sector strategy on STI, 2016–2021 [4]

Box 2.2 Chlamydia

Chlamydia accounts for 131 million STIs annually and is an important cause of infertility in women of reproductive age. It appears often as a coinfection with gonorrhea. The rate of infection is increasing in adolescents. However, the best strategy is yet to be defined. The WHO STI guideline (2016) recommends the following treatments [5].

Uncomplicated genital chlamydia:
- Azithromycin 1 g orally as a single dose
- Doxycycline 100 mg orally twice a day for 7 days
  Or one of these alternatives:
- Tetracycline 500 mg orally four times a day for 7 days
- Erythromycin 500 mg orally twice a day for 7 days
- Ofloxacin 200–400 mg orally twice a day for 7 days
  Anorectal chlamydial infection:
- Doxycycline 100 mg orally twice a day for 7 days over azithromycin 1 g orally as a single dose

Genital chlamydial infection in pregnant women:
- The WHO STI guideline recommends treatment with azithromycin over erythromycin
- The WHO STI guideline suggests treatment with azithromycin over amoxicillin
- The WHO STI guideline suggests treatment with amoxicillin over erythromycin

  Dosages:
- Azithromycin 1 g orally as a single dose
- Amoxicillin 500 mg orally three times a day for 7 days
- Erythromycin 500 mg orally twice a day for 7 days

Lymphogranuloma venereum:
The WHO STI guideline suggests treatment with doxycycline 100 mg orally twice daily for 21 days over azithromycin 1 g orally, weekly for 3 weeks.

Ophthalmia neonatorum:
The WHO STI guideline recommends treatment with azithromycin 20 mg/kg/day orally, one dose daily for 3 days, over erythromycin 50 mg/kg/day orally, in four divided doses daily for 14 days.

Box 2.3 Gonorrhea

Gonorrhea is one of the most common STIs worldwide and has a significant effect on morbidity and mortality. Together with chlamydia, it is one of the main causes of infertility in women of reproductive age. Gonorrhea has developed resistance to almost all medicines used for its treatment, which raises the prospect of untreatable gonococcal infection. Its spread and impact should therefore be controlled alongside systematic reporting and monitoring of antimicrobial resistance.

The WHO STI guideline (2016) recommends the following treatments [6]. The local AMR data should determine the choice of therapy.

Genital and anorectal gonococcal infection:
Dual therapy (one of the following)
- Ceftriaxone 250 mg intramuscular (IM) as a single dose PLUS azithromycin 1 g orally as a single dose
- Cefixime 400 mg orally as a single dose PLUS azithromycin 1 g orally as a single dose

Single therapy (one of the following)
- Ceftriaxone 250 mg IM as a single dose
- Cefixime 400 mg orally as a single dose
- Spectinomycin 2 g IM as a single dose

Oropharyngeal gonococcal infection:
Dual therapy (one of the following)
- Ceftriaxone 250 mg IM as a single dose PLUS azithromycin 1 g orally as a single dose

- Cefixime 400 mg orally as a single dose PLUS azithromycin 1 g orally as a single dose

  Single therapy
- Ceftriaxone 250 mg IM as single dose

  Gonococcal ophthalmia neonatorum: One of following
- Ceftriaxone 50 mg/kg (maximum 150 mg) IM as a single dose
- Kanamycin 25 mg/kg (maximum 75 mg) IM as a single dose
- Spectinomycin 25 mg/kg (maximum 75 mg) IM as a single dose

Box 2.4 Syphilis [7]

Recommendations

EARLY SYPHILIS (primary, secondary, or latent syphilis of not more than 2 years' duration)

  Adults and adolescents

In adults and adolescents with early syphilis, the STI WHO guideline recommends benzathine penicillin G 2.4 million units once intramuscularly over no treatment.
Remarks: This recommendation also applies to pregnant women, people living with HIV, people who are immunocompromised, and people at high risk of transmitting and acquiring STIs.

In adults and adolescents with early syphilis, the STI WHO guideline suggests using benzathine penicillin G 2.4 million units once intramuscularly over procaine penicillin G 1.2 million units 10–14 days intramuscularly.
When benzathine or procaine penicillin cannot be used (e.g., due to penicillin allergy) or not available, the STI WHO guideline suggests using doxycycline 100 mg twice daily orally for 14 days or ceftriaxone 1 g intramuscularly once daily for 10–14 days or azithromycin 2 g once orally.
Remarks: Doxycycline is preferred over ceftriaxone because of its lower cost and oral administration. Azithromycin is an option only when susceptibility to azithromycin is confirmed and resistance can be monitored. This recommendation also applies to people living with HIV, people who are immunocompromised, or people at high risk of transmitting and acquiring STIs. If the stage of syphilis is unknown, recommendations for persons with late syphilis should be followed.

  Pregnant women

In pregnant women with early syphilis, the WHO STI panel suggests using benzathine penicillin G 2.4 million units once intramuscularly over procaine penicillin 1.2 million units intramuscularly once daily for 10 days.
When benzathine or procaine penicillin cannot be used (e.g., due to penicillin allergy) or not available, the STI WHO guideline suggests using erythromycin 500 mg orally four times daily for 14 days or ceftriaxone 1 g intramuscularly once daily for 10–14 days or azithromycin 2 g once orally.
Remarks: Azithromycin is an option only when susceptibility to azithromycin is confirmed and resistance can be monitored. Erythromycin and azithromycin do not cross the placental barrier completely; therefore, treatment of the baby soon after delivery is necessary (see recommendations for congenital syphilis). Ceftriaxone is an expensive option and is injectable. Doxycycline should not be used in pregnant women.

LATE SYPHILIS (infection of more than 2 years' duration without evidence of treponemal infection)

  Adults and adolescents

In adults and adolescents with late syphilis or unknown stage of syphilis, the STI WHO guideline recommends benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over no treatment.
Remarks: This recommendation also applies to people living with HIV, people who are immunocompromised, or people at high risk of transmitting and acquiring STIs.

In adults and adolescents with late syphilis or unknown stage of syphilis, the STI WHO guideline suggests benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 million units once a day for 20 days.
When benzathine or procaine penicillin cannot be used (e.g., due to penicillin allergy) or not available, the STI WHO guideline suggests using doxycycline 100 mg twice daily orally for 30 days.
Remarks: This recommendation also applies to people living with HIV, people who are immunocompromised, or people at high risk of transmitting and acquiring STIs. Doxycycline should not be used in pregnant women (see recommendation for pregnant women).

Pregnant women

In pregnant women with late syphilis or unknown stage of syphilis, the WHO STI guideline suggests benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 million units intramuscularly once a day for 20 days.

When benzathine or procaine penicillin cannot be used (e.g., due to penicillin allergy) or not available, the STI WHO guideline suggests using erythromycin 500 mg orally four times daily for 30 days.

Remarks: Erythromycin does not cross the placental barrier completely; therefore, treatment of the baby soon after delivery is necessary (see recommendations for congenital syphilis). Doxycycline should not be used in pregnant women.

Infants

Infants with confirmed congenital syphilis (symptomatic or microbiological evidence) and infants who are clinically normal, but mother with syphilis was not treated, inadequately treated, or treated with non-penicillin

In infants with confirmed congenital syphilis or infants who are clinically normal, but the mother with syphilis was not treated, inadequately treated, or treated with non-penicillin, the WHO STI guideline suggests aqueous benzyl penicillin or procaine penicillin.

Dosages:
- Aqueous benzyl penicillin 100,000–150,000 U/kg/day intravenously for 10–15 days
- Procaine penicillin 50,000 U/kg/day single dose intramuscularly for 10–15 days

Remarks: If an experienced venipuncturist is available, aqueous benzyl penicillin may be preferred over intramuscular injections of procaine penicillin.

Infants who are clinically normal and the mother had syphilis and was adequately treated with no signs of reinfection

In infants who are clinically normal and the mother had syphilis and was adequately treated with no signs of reinfection, the WHO STI guideline suggests close monitoring of the infant over treatment.

Remarks: The risk of transmission of syphilis to the fetus depends on a number of factors, including titers and stage of infection, and therefore this recommendation is conditional. If treatment is provided, procaine penicillin 50,000 U/kg/day as a single dose intramuscularly for 10–15 days is an option.

Neglected Tropical Diseases

Key Point Summary
- Vector-borne infectious protozoa causing dermal complications such as lymphatic filariasis (LF) and leishmaniasis are to be targeted for elimination.
- Since the start of mass drug administration (MDA) for LF, the transmission has dropped and resulted in economic benefits. However, adverse events in the case of double infection by the *Loa loa* worm should be considered for revised local treatment and control strategies.
- The WHO strategy for LF is to interrupt transmission and target 70% of countries verified as free of LF by 2020, 30% under post surveillance, and full coverage and access to basic care for lymphedema. As for leishmaniasis, prevention and control with adequate diagnostic tools and vaccines are essential.
- The intervention and prevention strategies set up by the WHO for both protozoal infections overlap with regard to interrupting the chain of transmission, monitoring the burden of disease, vector control of sandflies and mosquitoes, environmental management and protection, and control of animal reservoirs.

Neglected tropical diseases (NTDs) are prevalent in 149 tropical and subtropical countries and affect more than 1 billion people annually. NTDs cover the following vector-borne infectious diseases: Chagas disease; dengue and chikungunya; dracunculiasis; human African trypanosomiasis; leishmaniasis; LF; and onchocerciasis. Other diseases such as buruli ulcer, echinococcosis, endemic treponematoses, foodborne trematodiases, leprosy, rabies, schistosomiasis, taeniasis, and trachoma are airborne, zoonotic, or transmitted vertically. This subsection highlights the vector-borne infectious diseases that cause dermal manifestations: leishmaniasis and LF.

Rationale

Leishmaniasis manifests in three forms: visceral, mucocutaneous, and the most common form, cutaneous leishmaniasis, caused by the protozoa *Leishmania* transmitted by phlebotomine sand-flies [8]. An estimated 900,000 to 1.3 million new cases and 20,000–30,000 deaths occur annually and affect the poorest people on earth. The disease is associated with malnutrition, population displacement, poor housing, a weak immune system, and lack of financial resources. Cutaneous leishmaniasis causes skin lesions, mainly ulcers, leaving life-long scars and serious disability. Mucocutaneous leishmaniasis leads to partial or total destruction of the nose, mouth, and throat membranes.

LF, a painful and profoundly disfiguring disease, commonly known as elephantiasis, is caused by the thread-like nematode worms *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*, and is transmitted by mosquitoes infected with microfilariae. More than 1.1 billion people in 55 countries worldwide, wherefrom 80% occur in African countries such as Angola, Cameroon, and Mozambique, are at risk for acquiring LF

and require preventive chemotherapy to stop the spread. Furthermore, an estimated 25 million men suffer from genital disease and 15 million are afflicted with lymphedema by this infection. Eliminating LF prevents unnecessary suffering and stigma while contributing to the reduction of poverty [9] (Figs. 2.3 and 2.4).

Strategy

Effective control of NTDs in general can be achieved when several public health approaches are combined. The WHA adopted a resolution with strategies to target the elimination of many diseases and eradication of at least two diseases by 2020. The WHA66.12 resolution calls on Member States to intensify and integrate measures and plan investments to improve the health and social well-being of affected populations [10].

The WHO Director-General requests to sustain the leadership of the WHO in the drive to overcome NTDs. The WHO control on leishmaniasis and LF involves supporting national control programs; raising awareness and advocacy of the global burden; development of evidence-based
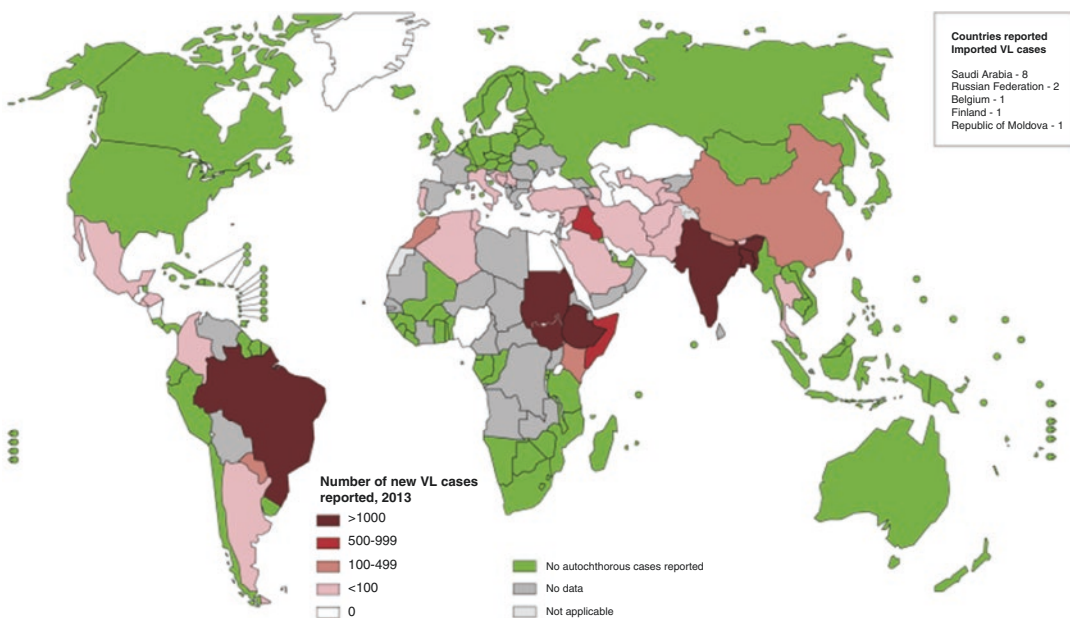
Fig. 2.3 Prevalence of Leishmaniasis (2014)
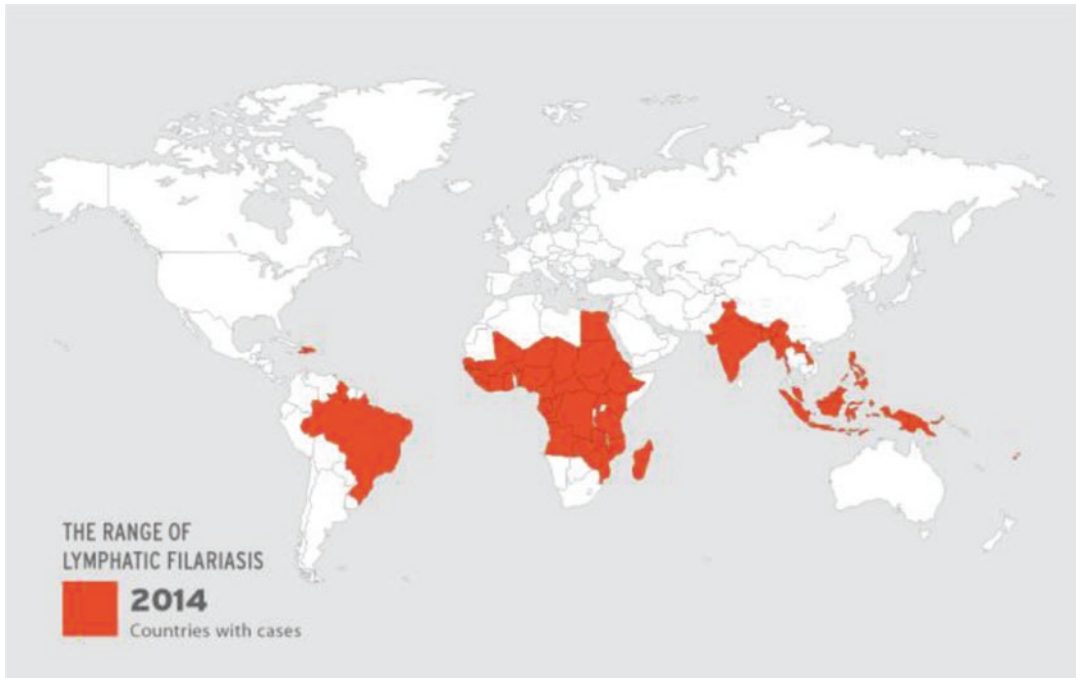
Fig. 2.4 Prevalence of LF (2014)

policy guidelines, strategies, and standards for prevention and control; monitoring implementation; technical support to Member States; and promoting research on effective leishmaniasis control as well as diagnostic tools and vaccines. In addition, the WHO strategy for LF is based on two key components: annual treatment of all eligible people in an endemic area, and alleviating the suffering caused by LF through increased morbidity management and disability prevention activities. Since the start of mass treatment, the transmission of LF in at-risk populations has fallen by 43% and the economic benefit is estimated at US$ 24 billion.

The Global Program to Eliminate Lymphatic Filariasis (GPELF), started in 2000 and continuing until 2020, delivers mass drug administration (MDA) LF endemic countries. The new strategy includes a protocol for stopping MDA and post-MDA surveillance. The programmatic steps taken to interrupt transmission are: (1) mapping geographical distribution of LF; (2) MDA; (3) surveillance; and (4) verification of elimination. The 2020 target for LF is to reach 70% of countries verified as free of LF and 30% under post

surveillance, and full geographical coverage and access to basic care for lymphedema in all countries. Moreover, the WHO calls for integrating national programs to eliminate LF and onchocerciasis within the African Program for Onchocerciasis Control (APOC).

Interventions

To control and prevent leishmaniasis and LF, a combination of intervention strategies are required which target the host, parasite, and vector, and sometimes also the animal reservoir [11, 12]. The key strategies for both infections are to reduce the prevalence of the disease and prevent disabilities and death by early diagnosis and case management. Early detection and treatment [13] of cases reduces the transmission and monitors the spread and burden of disease. For LF [14], morbidity management and disability prevention are required, alongside continuous access to care for LF patients with lymphedema to prevent disease progression to advanced stages. Simple measures of hygiene, skin care,

exercise, and elevation of affected limbs in LF help to prevent further progression.

Vector control is a key factor in reducing transmission and breaking the chain by controlling sandflies and mosquitoes. Methods such as insecticide sprays, insecticide nets, environmental management, and personal protection are to be used. Regarding the control of animal reservoirs, a complex intervention should be tailored to the local situation [15].

The treatment for LF is continued by MDA by expanding the coverage in non-participating countries and preventive chemotherapy for all LF endemic countries [16]. LF prevention is treated annually with a single dose of 400 mg albendazole with either 150–200 µg/kg ivermectin or 6 mg/kg, or annual preventive chemotherapy with diethylcarbamazine. However, coinfection with the *Loa loa* worm should be taken into consideration because of the adverse effect in ingesting ivermectin. The extensive treatment recommendations for various types of leishmaniasis are available at the following web page: http://www.who.int/leishmaniasis/research/978924129496_pp67_71.pdf?ua=1.

Partnership and collaboration with various stakeholders and other vector-borne disease control programs should be implemented together with education of the community and behavioral change interventions that are locally tailored. Furthermore, the financial burden should be lowered to make treatment and surgery possible for hydrocele or episodes of adenolymphangitis.

HIV and AIDS

Key Points Summary
- HIV Global Health Strategy for 2016–2020 is a priority for WHO and is based on accelerating actions and fast-tracking their responses
- WHO goal for HIV is the end of AIDS epidemic as a public health threat by 2030
- The Strategy 2020 global targets are: reduce new HIV infections and HIV-related deaths to fewer than 500,000 each and zero new infections among infants
- The five Strategic Directions are: information for action; interventions for impact; delivering for equity; financing for sustainability; and innovation for acceleration
- Unless intensified action occurs (hence the importance of fast-tracking), the HIV epidemics will see a rebound with current constant coverage

In May 2014, the 67th World Health Assembly requested a new strategy in the post-2015 development agenda whereby HIV continued to be a priority for the WHO [17]. The global health sector strategy on HIV/AIDS achieved 2015 targets of more than 15 million people on antiretroviral therapy (ART), with an estimated 7.8 million HIV-related deaths and 30 million new HIV infections averted since 2000. The 2030 Agenda for Sustainable Development adopted by the United Nations General Assembly in 2015 targeted the end of the AIDS epidemic by 2030. The WHO set forth to establish a new Global Health Strategy for HIV for 2016–2021, appraised during the 69th Health World Assembly in 2016 [18]. Full implementation of the draft strategy will contribute to the achievement of other sustainable development goals.

Global Health Sector Strategy on HIV, 2016–2021

Understanding that the actual steady-state response will see a rebound in new HIV infections and related deaths. Emphasis is laid on the need to fast-track the response to actions to prevent this rebound, outlining countries and WHO tasks to reach those goals [19]. The 2016–2021 strategy is based on five strategic directions to guide actions in achieving 2020 targets and goals (Fig. 2.5). Modeling undertaken by UNAIDS, estimates that an accelerated testing and treatment effort would:

Monitoring and Evaluation

Vision: Zero new infections, zero HIV-related deaths, and zero HIV-related discrimination in a world where people living with HIV are able to live long and healthy lives.

Goal: End of the epidemic as a public health threat by 2030.

2020 Targets: Reduction new HIV infection to less than 500 000; zero new infection among infants. Reduce HIV related deaths to below 500 000 90% people living with HiV tested, 90% treated, 90% virally suppressed.

Frameworks for action: Universal health coverage, the continuum of services, and a public health approach.

The three dimensions of UHC

STRATEGIC DIRECTION1

Information for focused action

The "who" and "where"

STRATEGIC DIRECTION 2

Interventions for impact

The "what"

STRATEGIC DIRECTION 3

Delivering for equity

The "how"

STRATEGIC DIRECTION 4

Financing for sustainability

The financing

STRATEGIC DIRECTION 5

Innovation for acceleration

The future

STRATEGY IMPLEMENTATION:
Leadership, Partnership, Accountability, Monitoring & Evaluation

COUNTRY ACTION

Country Partner Action

WHO ACTION HQ, REGIONS AND COUNTRIES

Global Partner Action

Fig. 2.5 Outline of the draft global health sector strategy on HIV, 2016–2021

Fig. 2.6 Projections for decline in HIV-related deaths
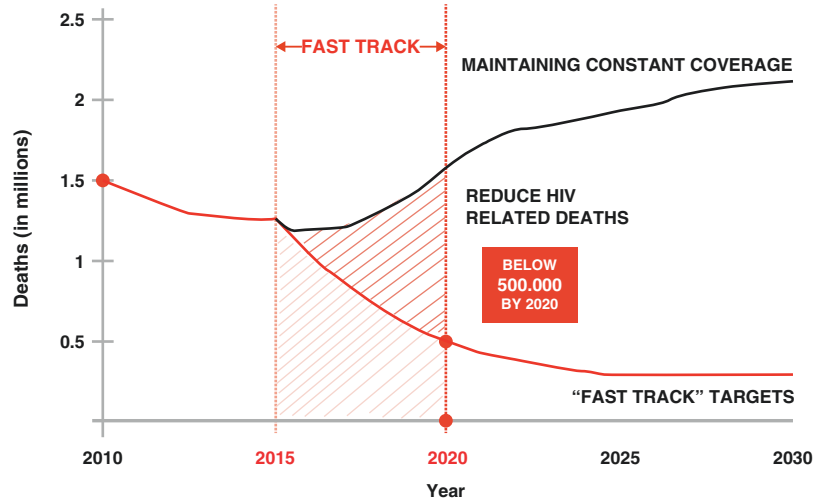
- Avert 28 million HIV infections between 2015 and 2030
- Avert 21 million AIDS-related deaths between 2015 and 2030 (Fig. 2.6)
- Avoid US$ 24,000 million of additional costs for HIV treatment
- Enable countries to reap a 15-fold return on their HIV investments

Strategic Direction 1: Information for Focused Action (What is the Situation?)

Focuses on the need to understand the HIV epidemic and response as a basis for advocacy, political commitment, and national planning as well as resource mobilization and allocation and program improvement. WHO guidelines recommend adoption of 50 national indicators [20] (see suggested readings, "Global Health Sector Strategy on HIV, 2016–2021"), of which the following 10 are for global monitoring (Fig. 2.7).

Strategic Direction 2: Interventions for Impact (What Services Should be Delivered?)

Addresses the first dimension of universal health coverage by describing the essential package of high-impact interventions that need to be delivered along the continuum of HIV services.

The following interventions should be included in an HIV prevention package:

- Male and female condoms
- Harm reduction for people who inject drugs
- ART-based prevention
- Vertical transmission prevention
- Voluntary male circumcision
- Injection and blood safety
- Behavioral change interventions
- Prevention and management of gender-based and sexual violence

HIV testing should be expanded, focusing on populations carrying the highest risk for HIV infection and transmission, with appropriate counseling and links to care. This is needed for the expansion of ART therapy [21, 22] to achieve the 90% people living with HIV (PLHIV) treatment goal (see Box 2.5 for first-line therapy regimens). Besides expanding ART, action should be taken to prevent and manage coinfections such as tuberculosis, hepatitis B and C, and HIV drug resistance. Chronic care for PLHIV should be person centered.

Box 2.5 First-Line Regimens (Adults and Adolescents)

Pre-exposure prophylaxis: Tenofovir (TDF)

Post-exposure prophylaxis: TDF + lamivudine (3TC) (+ lopinavir/ritonavir or atazanavir/ritonavir if possible)

ART Therapy: TDF + 3TC + efavirenz (EFV)
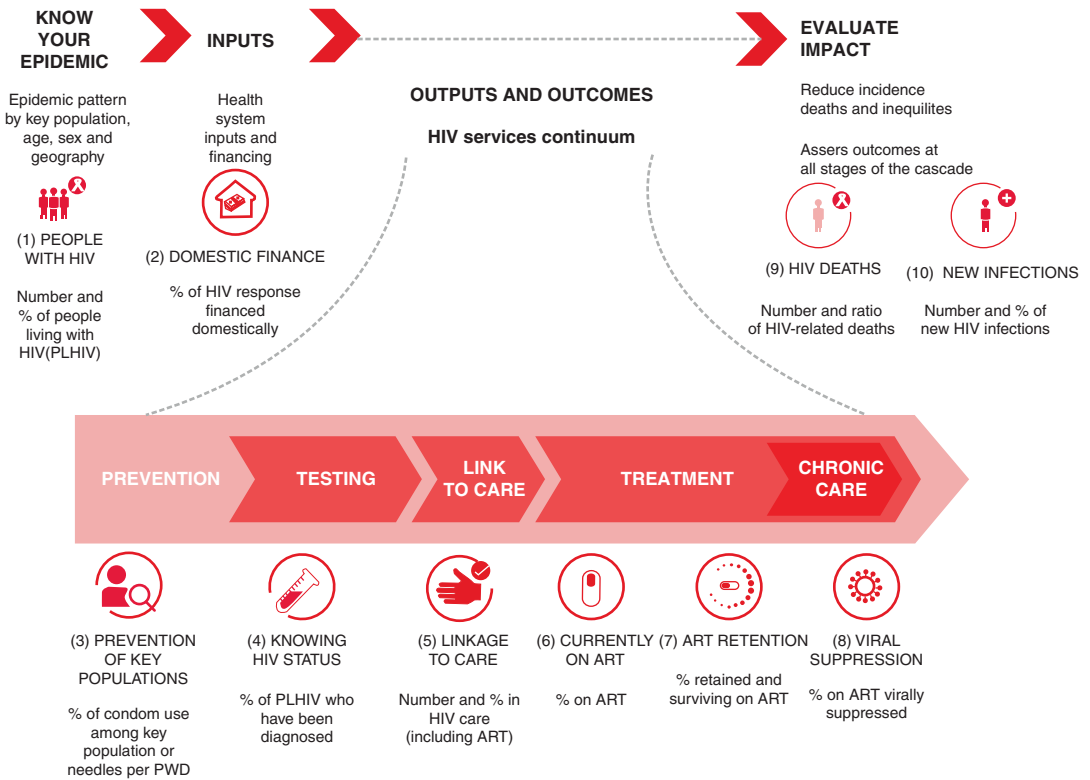
Fig. 2.7 Key indicators for monitoring the HIV response across the continuum of HIV services and including the HIV care cascade

Strategic Direction 3: Delivering for Equity (How Can These Services be Delivered?)

Addresses the second dimension of universal health coverage by identifying the best methods for delivering the continuum of HIV services to different populations and in different locations. Special focus should be fixed on addressing key populations (at increased risk of HIV regardless of the local epidemic context): men who have sex with men, people who inject drugs, people in prison and other closed settings, sex workers, and transgender persons.

Strategies for achieving equity include decentralization of care, differentiated care (based on stage of HIV disease, stability of treatment and special care needs), linking HIV with tuberculosis services, community engagement and task shifting, and providing chronic care for PLHIV. Countries should also end policies and practices that reinforce stigmatization and discrimination.

Strategic Direction 4: Financing for Sustainability (How Can the Costs of Delivering the Package of Services Be Covered?)

Addresses the third dimension of universal health coverage by identifying innovative models and approaches for financing HIV responses and reducing costs without incurring financial hardship: essential HIV services should be provided free of charge. Reducing costs also mean improving efficiency of service delivery, such as decentralization, service linkage, and task shifting. Other strategies include fostering generic competition on ART drugs, applying pro-access terms of the Medicines Patent Pool,

and appropriate use of the provisions in the Agreements on Trade-Related Aspects of Intellectual Property Rights regarding flexibilities to protect public health.

However, it is acknowledged that investments in HIV will need to grow if long-term control of the epidemic is to be achieved; therefore, countries need to develop strong investment cases for HIV.

Strategic Direction 5: Innovation for Acceleration (How Can the Trajectory of the Response be Changed?)

Identifies those areas where there are major gaps in knowledge and technologies, and where innovation is required so that actions can be accelerated and 2020 and 2030 targets achieved. Research and innovation provide the tools and knowledge that can change the trajectory of the HIV response. Innovation is also required to use existing tools more efficiently and to adapt them for different populations.

Key areas for innovation are: optimizing HIV prevention; optimizing HIV testing and diagnostics; optimizing HIV medicines and treatment regimens; and optimizing service delivery.

Strategy Implementation

Finally, effective implementation of this strategy depends on collaboration between all involved parties, in which the WHO plays an important convening role. Monitoring and evaluation are done at global and regional/country level goals (Fig. 2.6), while applying WHO results-based management and UNAIDS accountability frameworks.

Key Points Summary
- Once leprosy was eliminated as a public health problem globally in 2000, WHO global leprosy strategy focused on reducing leprosy-related disabilities
- 2016–2020 WHO Global Leprosy Strategy focuses on promoting early diagnosis to reduce leprosy burden

- The Strategy 2020 targets are: zero new children diagnosed with leprosy and visible deformities, <1 per million newly diagnosed leprosy patients with visible deformities; and zero countries with legislation allowing discrimination on leprosy
- The Program five key operational strategies are: focus on early detection; increased detection and coverage; universal contacts screening; uniform leprosy treatment; and interventions against stigma and discrimination

Leprosy

Leprosy was eliminated as a public health problem globally in 2000 (defined by the WHO as prevalence less than 1 per 10,000 population). The 2011–2015 WHO strategy for leprosy focused on control with early diagnosis to reduce leprosy-related disabilities. The global leprosy strategy for 2016–2020 continues to reinforce early detection to reduce the burden of leprosy, while accelerating actions toward the vision of a leprosy-free world [23]. The strategy general overview, its three pillars and their core areas of interventions, are displayed in Fig. 2.8.

There are five key strategic operational changes in the 2016–2020 plan along with target indicators:

1. Focus on early detection to prevent disabilities, with special focus on children. The target is zero disabilities among new pediatric patients (<15 years of age) by 2020. For countries that do not detect grade 2 disability (G2D) among pediatric patients, the target shall be zero pediatric cases.
2. Increased detection, coverage, and access to treatment for high-risk groups and marginalized populations. The target is an incidence of G2D of less than 1 per million population.

VISION

- ⊙ Zero disease
- ⊙ Zero transmission of leprosy infection
- ⊙ Zero disability due to leprosy
- ⊙ Zero stigma and discrimination

GOAL

Further reduce the global and local leprosy burden

TARGETS

INDICATORSA	2020 target
Number of children diagnosed with leprosy and visible deformities	0
Rate of newly diagnosed leprosy patines with visible deformities	<1 per million
Number of countries with legislation allowing discrimination on basis of leprosy	0

PILLARS AND COMPONENTS

1. Strengthen government ownership, coordination and partnership

- Ensuring political commitment and adequate resources for leprosy programmes.
- Contributing to universl health coverage with a special focus on children, women and underserved populations induding migrants and displaced people.
- Promoting partnerships with state and non-state actors and promote intersectoral collaboration and partnerships at the international leveal and within countries.
- Facilitating and conducting basic and operational research in all aspects of leprosy and maximixe the evidence base to inform policies. strategies and activities.
- Strengthening surveillance and health information systems for programme monitoring and evaluation(induding geographical information) systems)

2. Stop leprosy and its complications

- Strengthening patient and community awareness on leprosy.
- Promoting early case detection through active case finding (e.g campaigns) in areas of higher endemicity and contact management.
- Ensuring prompt start and adherence to treatment, including working towards improved treatment regimens.
- Improving prevention and management of disabilities.
- Strengthening surveilance for antimicrobial resistance including laboratory network.
- Promoting innovative approaches for training, referrals and sustaining expertise in leprosy such eHealth.
- Promoting interventions for the prevention of infection and disease.

3. Stop discrimination and promote inclusion

- Promoting societal inclusion through addressing all forms of discrimination and stigma.
- Empowering persons affected by leprosy and strengthen their capacity to participate actively in leprosy services.
- Involving communities in actions for improvement of leprosy services.
- Promoting coalition building among persons affected by leprosy and encourage the integration of these coalitions and or their members with other community-based organizations.
- Promoting access to social and financial support services, e.g. to facilitate income generation, for persons affected by leprosy and their families.
- Supporting community-based rehabilitation for people with leprosy related disabilities.
- Working towards abolishing discriminatory laws and promote policies facilitating inclusion of persons affected by leprosy.

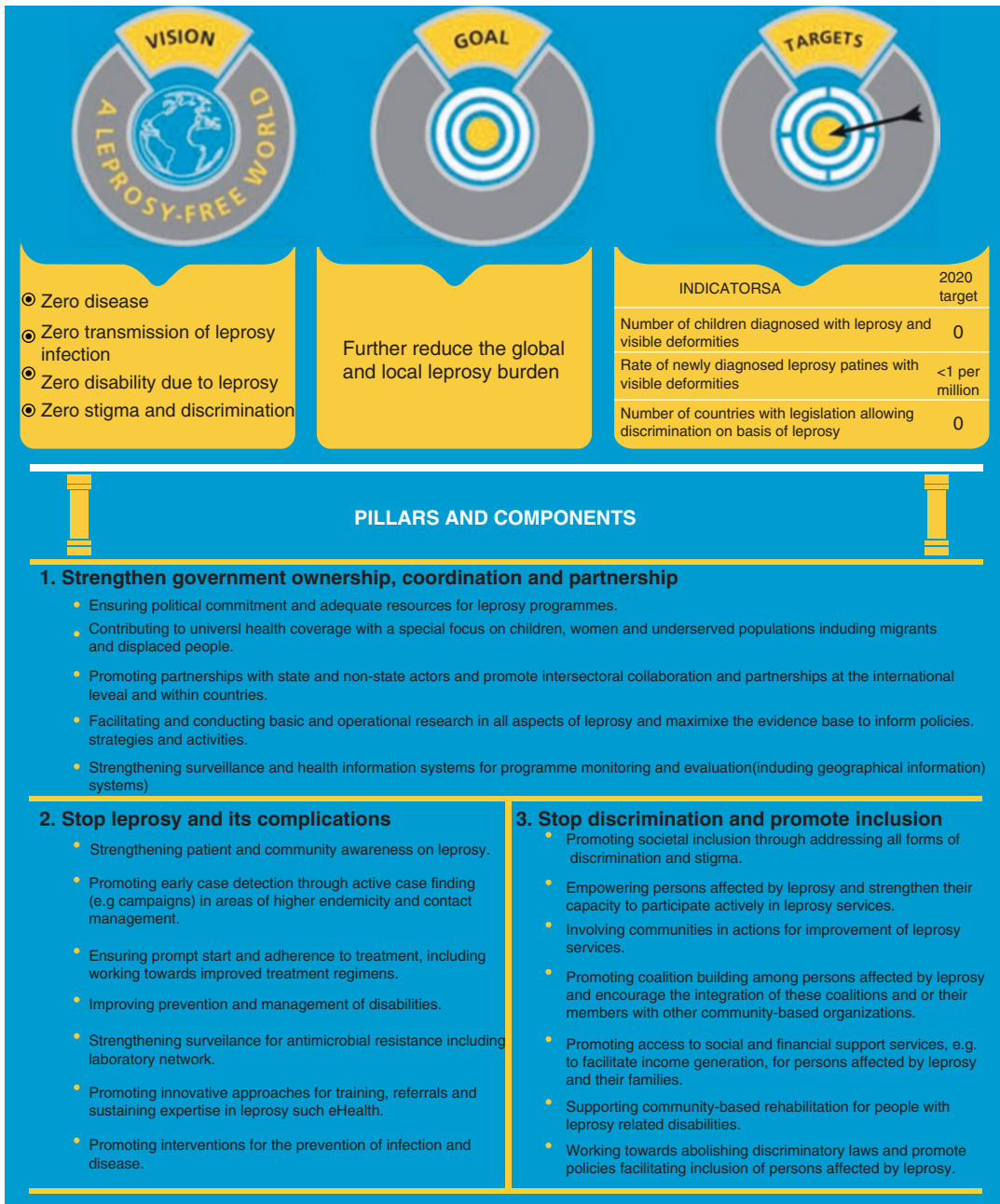**Fig. 2.8** WHO 2016–2020 Global Leprosy Strategy overview (From Global Leprosy Strategy: accelerating towards a leprosy-free world. World Health Organization, Regional Office for South-East Asia, 2016)

3. National plans to ensure screening of all close contacts. The target is to have all household contacts screened.

4. Promote steps toward the use of shorter and uniform treatment regimens for all types of leprosy.

5. Incorporate specific interventions against stigma and discrimination due to leprosy. The target is zero countries with legislation allowing discrimination on the basis of leprosy.

Other relevant program performance indicators for routine monitoring are (always disaggregated by sex and age group when applicable):

- Annual new case detection and new case detection rate per 100,000 population
- Point prevalence of leprosy per 10,000 population
- Number and/or proportion of relapses among all leprosy notified cases
- Completion rate of multidrug therapy (MDT) in all cases
- Availability of web-based, case-based reporting system allowing disaggregation by age, sex, place of residence, and other relevant criteria
- Proportion of contacts screened among registered contacts
- Proportion of patients evaluated for disabilities at the end of treatment
- Proportion of patients having reactions among new cases, disaggregated by bacillary load (paucibacillary or multibacillary)
- Proportion of persons affected by leprosy in self-care support programs among patients with grade 1 disabilities and G2D
- Norms and/or regulations facilitating the inclusion of persons affected by leprosy and their communities
- Affected persons or associations of affected persons with a role in care
- Presence of a partnership with the private sector for case detection/referral, care, and/or social support
- Number and proportion of drug-resistant cases

It has also been recognized that more coordinated efforts for research with regard to new diagnostic tools, drugs, and tools to manage complications are needed.

The WHO recommended MDT regimens are shown in Box 2.6. Treatment should be provided in blister packs that make clear distinctions between once-a-month and once-a-day drugs for the patient.

Box 2.6 Adult MDT regimen

–	PB: 6 months	MB: 12 months
Monthly	Rifampicin 600 mg + dapsone 100 mg	PB regimen + clofazimine 300 mg
Daily	Dapsone 100 mg	PB regimen + clofazimine 50 mg

Skin Diseases in Primary Care

Key Points Summary
- Some non-governmental organizations, such as the International Society of Dermatology, have developed public health task forces and programs to promote skin health
- Although the WHO has no specific public health strategies for general skin diseases in primary care, it has issued simple and practical clinical guidelines in the Integrated Management of Adolescent and Adult Illness (IMAI) for such diseases

The International Society of Dermatology set the task force "Skin Care for All: Community Dermatology" [24] to promote general skin health, stating that public health strategies have not been sufficiently inclusive of skin care. The program focuses on low-cost interventions, relying on self-help and low technology, while educating a workforce for skin care among primary care health workers, nurses, and physicians, facilitating delivery of skin care to those in need. The task force is responsible for the creation of the Regional Dermatology Training Centre in Tanzania, with several dermatology graduates serving in Sub-Saharan Africa; and a 1-day training course for health center personnel in Mali for recognition and management of the three most commonest skin conditions: impetigo, superficial fungus, and scabies. It also emphasizes the "look good feel good factor" concept in advocating skin care, and promotes social marketing such as "Natural is Beautiful" to prevent the use of creams containing harmful agents.

Table 2.1 Use this table if lesion red, tender, warm, pus, or crusts (infected skin lesion—consider this in all skin lesions)

Sign	Classify as	Treatments
• Fever or • Systemically unwell or • Infection extends to muscle	**Severe soft tissue or muscle infection**	• Refer to hospital • Start IV/IM antibiotics (if not • available, give oral cloxacillin) • Consider HIV-related illness
• Size >4 cm or • Red streaks or • Tender nodes or • Multiple abscesses	**Soft tissue infection or folliculitis**	• Start cloxacillin • Drain pus if fluctuance • Elevate the lump • Follow up next day
• Only red, tender, warm, pus or crusts–none of the signs in the pink or yellow row	**Impetigo or minor abscess**	• Clean sores with antiseptic • Drain pus if fluctuance • Follow up in 2 days

Adapted from Integrated Management of Adolescent and Adult Illness. WHO; 2004

While the WHO has not developed public health strategies for general skin diseases as seen in primary care (aside from specific diseases with an important burden such as leprosy), it has issued the IMAI in 2004, with interim guidelines for primary care workers on the diagnosis and treatment of several skin diseases and conditions (see suggested readings, "Skin Diseases in Primary Care"). These guidelines are based on several algorithms for easily defining the type of skin problem (e.g., lump, itching lesion, patch, infected lesion) and tables for prompt diagnosis or classification of each type of problem along with its specific management (see Table 2.1 for an example). They should be validated in primary care intervention studies.

Future Perspectives

The WHO will continue to be a leading public health organization at international level. Its importance will depend on the capability of the new Director General, to be elected in May 2017, to mobilize financial and human resources and to continue to deliver high-level strategies and products for its member countries. The use of the GRADE methodology to develop international guidelines has been questioned as too strict and expensive. A challenge to be faced is to maintain the present high scientific standard of developing a modified and user-friendly methodology.

STIs, especially syphilis, will decrease in incidence and prevalence but will continue to be a major public health concern. The reasons for this include the lack of affordable tests to identify asymptomatic infections, difficulties in reaching sexual partners, and weak health systems not providing extended access to STI services of adequate quality to all in need.

The WHO strategy will contribute to interrupt the transmission of LF and the targets will be probably be reached (70% of countries verified as free of LF by 2020, 30% under post surveillance and full coverage and access to basic care

for lymphedema). Leishmaniasis will be more difficult to eliminate, as the diagnostic tools and vaccines are yet to reach optimal performance.

The WHO goal for HIV, the end of AIDS as a public health threat by 2030, probably will not be reached because the present international environment is not intensifying actions as required and, as is mentioned in the strategy, necessary innovations are still not in the pipeline.

Considering that leprosy was eliminated as a public health problem globally, the WHO global leprosy strategy focuses on reducing leprosy-related disabilities. This will be more difficult given the fact that disabilities are not always related to active disease. Moreover, it will be difficult to reach the ambitious target of zero new children diagnosed with leprosy and visible deformities. The strategy focuses on early detection, increased detection and coverage, universal contacts screening, uniform leprosy treatment, and interventions against stigma and discrimination. Most of the strategies rely on coverage and quality of health systems, which are not performing optimally at this stage in the most affected countries.

In relation to skin diseases a global strategy is needed, targeting primary health care, using simple and practical quality clinical guidelines. These guidelines, based on IMAI work, need to be further developed and field-tested before wide dissemination. A discussion on the role of dermatologists at different levels of health systems needs to be conducted with the participation of specialists, universities, and public health authorities.

Glossary

3TC	Lamivudine
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ATV/r	Atazanavir/ritonavir
EFV	Efavirenz
HIV	Human immunodeficiency virus
LPV/r	Lopinavir/ritonavir
PLHIV	People living with HIV
PWID	People who inject drugs
TDF	Tenofovir
WHO	World Health Organization

G2D	Grade 2 disability
MB	Multibacillary
MDT	Multidrug therapy
PB	Paucibacillary

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The User of the Public Dermatology Service

3

Heitor de Sá Gonçalves, Maria Araci de Andrade Pontes, and Gerson Oliveira Penna

Key Points

- Skin diseases are responsible for approximately one-quarter of medical appointments in primary care.
- Patients with cutaneous problems experience a reduction in their quality of life that often goes beyond other non-dermatological conditions.
- Social and demographic characteristics of the population using public dermatology services are essential to direct and plan public health policies.
- Nosologic profile in dermatology depends on many variables such as gender, age, socioeconomic status, and access to health services, among others.
- Health professionals should be able to observe and recognize symptoms of the cutaneous complaints more prevalent in the population they care for.

Introduction

Skin diseases are one of the main reasons why people seek medical care and are responsible for approximately one-quarter of primary care appointments, both in tropical countries and developed nations [1]. In fact, in the United States they are among the 15 medical conditions whose prevalence and cost have increased the most between 1987 and 2000, with approximately one in every three people in the country reporting cutaneous problems [2].

The importance of skin health is underestimated because of the chronic nature and low lethality of most cutaneous diseases, which results in their not being considered important health problems. However, skin conditions can be precursors to considerable physical and psychological deficiencies, making them a public health problem of great magnitude. Important examples of these diseases can be cited, such as Hansen's disease, psoriasis, vitiligo, lupus, genodermatoses, atopic childhood dermatitis, and skin cancer, especially melanoma.

A study conducted in Sweden, with a random sample of 8,000 individuals, assessed the impact of skin conditions on the quality of life of this population from an epidemiologic perspective. The subjects were aged between 20 and 84 years, and 20.5% reported skin problems and/or the use of topical medications, with a higher frequency among women [3].

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Another survey, conducted in France in 2002, evaluated the prevalence, management, and impact of dermatological diseases from the patient's point of view. Of a total of 25,441 subjects, 18,137 (71.3%) returned the questionnaire. Of these, 86.8% reported at least one skin problem from birth, and 43.2% had had a skin disease in the previous 24 months. For 28.7% of the respondents, their dermatological problem had impaired their quality of life [4].

Patients with cutaneous complaints experience a reduced quality of life that often goes beyond other non-dermatological conditions, including restricted mobility, intense pruritus, and physical and psychological discomfort; the physical characteristics of the diseases related to contagion and deformity may even lead to the social segregation of individuals. Such restrictions undermine activities of daily life and have a great impact on the patient's sense of well-being [2]. Acne vulgaris and psoriasis, for example, have been linked to suicidal thoughts [5].

Although skin problems are common in the population, there is little information on the profile of users of public dermatology health services. Data on the dermatological care provided in public health services are critically important to identify and monitor the impact of dermatological diseases on the health of the population, as well as the user profile of those afflicted, with a view toward planning the treatment, prevention, and promotion of such maladies, especially among the most vulnerable population groups.

State of the Art

Health Services

The World Health Organization defines a health system as a network of organizations, people, and actions whose primary objective is to promote, restore, or maintain health [6]. This includes the public, private, and voluntary bodies that contribute to the delivery of essential health services, working to fulfill the mission of guaranteeing a healthy population. The responsibility for the public's health in each country lies with specific

agencies at different levels of management (municipal, state, federal, and international).

Health systems can vary substantially between countries, especially in terms of the responsibility for how the health services offered to the population are financed. There are primarily five forms of financing for services offered to the population (Box 3.1), although most countries offer a mixed model.

> **Box 3.1. Modalities for Financing Health Systems**
> Financing of Health Systems
>
> A. Federal, state, or municipal taxation
> B. Social health insurance
> C. Private health insurance
> D. Direct out-of-pocket payments
> E. Donation to charity

In 1948, the Ministry of Health of the United Kingdom created the British national health system (National Health Service) as a regionalized and hierarchical systemic organization of health services, arranged by level of complexity with a defined geographical base. This model has influenced and guided the organization of health services in various countries around the world. The system is structured into a stratified model. The levels of complexity are used to establish a network of services, according to the characteristics of care and the degree of specialization of the services provided [7].

The elements implied in the definition of the levels of care include the technological material used (diagnostic and therapeutic machines and equipment), staff training, and the morbidity profile of the target population. The possible arrangements of these three elements in health systems depend on the system's characteristics in terms of the financial and material means, the personnel structure available, and the health policies implemented in each country.

The primary care level represents the first contact patients have with the health system and should be capable of resolving a large portion of the health problems they present, through

non-specialized outpatient care and low-density technological clinical activities aimed at the promotion, prevention, and restoration of health. Staff qualifications for this level involve a general and comprehensive training with an emphasis on family health. It is estimated that between 85% and 90% of the patients seeking primary care are likely to be resolved at this level.

The secondary level develops activities in basic medical specialties (general medicine, pediatrics, gynecology-obstetrics, and general surgery) and strategic specialists in the form of outpatient appointments, hospitalization, and emergency and rehabilitation care. These services should have equipment with an intermediary degree of technological innovation to deal with situations that are not absorbed by the primary level.

Highly advanced technology and more specialized personnel are concentrated at the tertiary level, which is responsible for solving the more complex situations.

The Brazilian health system is composed of a free public system (Unified Health System, SUS) that cares for most of the population. A private system, or Supplementary Health System, managed by health insurers is available and can be acquired individually or as a benefit offered by employers. In 2008, the private system of supplementary health covered 25.9% of the Brazilian population [8].

The financing of SUS counts on resources from the three spheres of government (municipal, state, and federal). When considering the services according to the level of care, in general it can be said that the federal sphere concentrates on tertiary care, the state on tertiary and secondary care, and the municipal level on primary and secondary care.

Within this stratified model of care, appointments for dermatological problems are initially carried out by general practitioners in primary care. All health professionals should be able to observe and recognize the symptoms of the cutaneous complaints prevalent in the population they care for. However, most of these professionals do not feel qualified to diagnose and treat these infections and limit themselves to referring patients to dermatologists at the secondary level.

The Social and Demographic Profile of the Users

There are few data on the demographic and social characteristics of the population that uses outpatient services in the health system, despite these data being essential to direct and plan public health policies. It is even more difficult to find data relating specifically to the characteristics of dermatology patients.

A national inquiry promoted by the Brazilian Ministry of Health periodically analyses the profile of the users of the health service, using, among others, data referring to the proportion of individuals who looked for or reported having used the health service in the previous 2 weeks and those who stated they had been admitted to hospital in the previous 12 months. Women are responsible for most of the demand for health services (17% compared with 12% among men) and there is an increase in this demand due to age (12% aged 0–14, 14% between 15 and 59 years, and 23% over 60 years) [8].

A population-based study with a sample of 12,402 Brazilians aged between 20 and 59 years, living in urban areas, showed a prevalence of outpatient care in public health services of 53.6% in the 3 months prior to the interview. Women represented 55.1% of the sample and about one-third (31.8%) were aged between 20 and 29 years, with a mean age of 37.4 years. More than half (51.5%) were in social class C [9].

Few studies show the user profile of public dermatology services, but it seems that this is similar to the population that seeks public health services in general; they are predominantly women, blacks, and have a low socioeconomic and educational level [10].

A multicenter, retrospective study addressing patients who seek dermatological care in four specialized outpatient services in Australia observed, over 7 months, a total of 9,639 visits by a total of 4,875 patients. In this sample there was a predominance of males (51.4%). The mean age was 48 years (50 years for men and 45 years for women; $p = 0002$) [11].

In England, more than 50% of the population reported a skin disease in the previous 12 months,
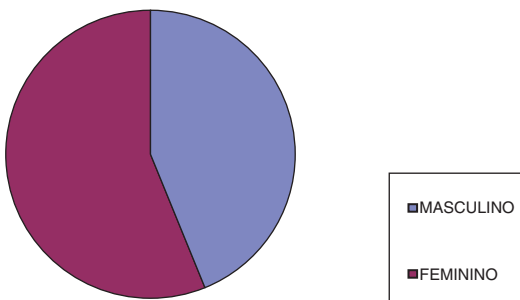
and 24% required medical intervention to care for dermatological problems every year. Among users of dermatology services there was a predominance of women (57.6%) in all age groups, but especially between 20 and 39 years [12].

A survey conducted by the Brazilian Society of Dermatology in 2006, with data for 57,343 patients, also showed a predominance of females (66.5%) in all age groups. The mean age was 37.4 years (35.3 years for men and 38.4 years for women). Schooling was the most divergent aspect when comparing patients treated in the public sector with those in the private sector: 65.7% of patients treated in the public sector and 27.6% of those cared for in the private sector had not completed secondary education [13].

Data from a public referral service in dermatology in the Northeast of Brazil, state of Ceará, collected from a random sample of 1,530 patients who attended the service for the first time between November 2015 and March 2016, showed a predominance of women (56%).The age distribution showed no significant differences between groups (0–20, 19%; 20–40, 26%; 40–60, 25%; >60, 31%). Most were residents of the state capital, Fortaleza (68%). These data can be viewed in Graphs 3.1 and 3.2 (unpublished data).
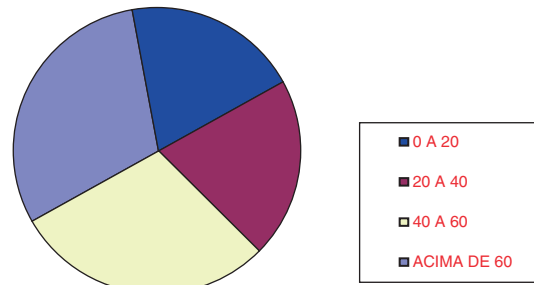
The predominance of females in dermatological appointments may be related to the greater care take with their skin in particular, also reflecting women's greater concern with health in gen-

DISTRIBUTION BY AGE

Graph 3.2 Distribution of users by age (Source: Dona Libânia Dermatological Center, 2016)

eral. On the other hand, the larger demand by females for health services may be related to the socioeconomic and labor structure in Brazil, especially in the North and Northeast regions, where there are more women without formal employment who therefore have more time available to use the health service.

The Nosological Profile of Users

The epidemiological data of the population who use the public dermatology health services are influenced by many factors, such as socioeconomic profile, educational profile, housing and hygiene, dietary habits, and the circumstances of access to health services. It is possible to alter these data when analyzing the patient profile according to the cutaneous pathology being presented, since there are diseases that mainly affect certain age groups, such as acne, which predominates in adolescence, and skin cancer, prevalent in older age groups.

Among the infectious and parasitic diseases that most often affect the skin are the ectoparasites (scabies, larva migrans, and pediculosis), superficial fungal infections (tineas, candidiasis, and tinea versicolor), the pyoderma (impetigo and folliculitis), and dermatoviruses (herpes, molluscum contagiosum, and warts). Hansen's disease and American tegumentary leishmaniasis are dermatological diseases with compulsory notification, the former because of its magnitude,

DISTRIBUTION BY SEX

Graph 3.1 Distribution of users by sex (Source: Dona Libânia Dermatological Center, 2016)

preeminence, and its ability to cause incapacity and deformity, as well as being a transmissible disease that can be treated and controlled [14]. The notification of cases of American tegumentary leishmaniasis in all its forms is obligatory, not only because of the disease's high incidence and wide geographical distribution but also because of the possibility of it causing destructive wounds [14]. Notable among the noninfectious skin diseases are acne, psoriasis, vitiligo, skin cancer, contact dermatitis (as a work-related condition), and atopic dermatitis, particularly in children. There may or may not be a determinant socioeconomic profile for each of the aforementioned conditions.

Scabies affects all races, ages, and social classes, although it is predominant in adult individuals on a low income. Larva migrans predominates in children between 5 and 15 years from low-income families, who walk barefoot on contaminated land, as well as children from all social classes who frequent beaches where stray dogs and cats live. Pediculosis is prevalent in children between 3 and 10 years of both sexes from low-income families.

Tinea versicolor affects adults of both sexes after puberty, predominantly in hot and humid climates. The distribution of dermatophytoses (tineas) is influenced by population factors such as gender (more common in males) and age (tinea scalp is more common in children; tinea of the foot and inguinocrural tinea are more common in adults).

Impetigo is most common in children, having no gender preference. Folliculitis can affect all age groups, but some conditions have a higher affinity for certain population groups, such as hidrosadenitis, which predominates in postpubescent women, or keloid folliculitis, which mainly affects black men.

The prevalence of herpes simplex is also determined by epidemiological factors. Primary herpetic gingivostomatitis is most commonly observed in children, while oral or relapsing genital herpes manifests itself mainly in adults. Molluscum contagiosum is more common in children and can occur in adults with immunodeficiency, particularly AIDS patients. Warts can occur at any age but are more common in children and young adults.

Hansen's disease affects people of both sexes and all ages. It tends to predominate in males and the population on a low socioeconomic level, presenting a lower incidence in children younger than 15 years. Although the global trend is a reduction in new cases, the service area in question (northeastern Brazil) maintains incidence rates at very high levels.

American tegumentary leishmaniasis is found in all of the Brazilian states, with a tendency to affect people who live in rural areas and locations with old deforestation, as well as a small percentage of cases located in the urban periphery. Initially predominantly young male adults were affected; nowadays it has become more frequent to find cases in people of all sexes and ages.

As a disease of the pilosebaceous follicles, acne tends to manifest predominantly in adolescents and young adults. Although almost all teenagers develop acne, genetic and external factors (e.g., emotional stress, female androgenic syndromes) can influence both the severity and recurrence of the disease.

The prevalence of psoriasis is around 2% of the population. The disease also affects both sexes and appears at any age, although peak incidence is between 20 and 30 years, with a second peak between 50 and 60 years.

Vitiligo affects about 1% of the population and has a universal distribution, affecting all age groups and both sexes. In 30% of cases there is a family history of the condition.

Nonmelanoma skin cancer (basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)) generally occurs in male individuals older than 40; the predisposing factors are exposure to sunlight and fair skin. These cancers are rare in black individuals.

To check the frequency of the main diagnoses in the practice of dermatologists in Brazil, the Brazilian Society of Dermatology conducted a survey with 932 dermatologists selected from the register of 4,400 associates, working in both the public and private sectors. In addition to private services, the sample also included 49 SUS outpatient services that offer medical residency

programs in dermatology, distributed in all regions of the country. The diagnoses relating to outpatient dermatological care were recorded during a week in May 2006 and provide a picture of the demand for specialized dermatology care in Brazil, both in the public and private systems [13]. As expected, the inclusion of private services has led to some bias regarding diseases with a higher diagnostic incidence when comparing these data with the incidence of diagnoses in the public service alone.

The results were based on 57,343 dermatological appointments. During the study period (1 week) there were more than 1,000 different diagnoses, which is to be expected as a result of appointments with specialists that involve less common diseases whose diagnosis and monitoring need specialized care. Acne was the main reason for appointments and amounted to 14% of cases, followed by superficial mycoses (8.7%), pigmentation disorders (8.4%), and actinic keratosis (5.1%). The study also examined the proportion of return visits among the 25 most frequent causes, with Hansen's disease (78%), psoriasis (68%), and vitiligo (64%) initiating the most subsequent visits. Hansen's disease was rated the 20th cause throughout the country but the fourth in the Center-West Region.

The distribution of diagnoses by age group maintains acne as first cause of visits to the dermatologist both in those younger than 15 years (13.9%) and those aged between 15 and 39 years (26.6%). Superficial mycoses remain among the five most frequent diagnoses in all age groups, although the distribution of subtypes reflects the model of referral to specialists in more complex cases, especially onychomycosis (42% of superficial mycoses) and a low proportion of candidiasis.

Bearing in mind that acne has a significant psychological impact, the high frequency of acne diagnoses, even considering the leading role of the private sector in making such diagnoses, shows the relevance of the public service offering not only clinical treatment but also psychological support and health education initiatives aimed at the teenage population.

More than one-quarter (26.8%) of patients older than 65 were diagnosed with actinic keratosis or BCC, reinforcing the need for skin cancer prevention measures in the country. Interestingly, diagnoses of BCC predominated in the public sector, whereas in the private sector actinic keratosis was more frequent. This may reflect the delay in diagnosis and treatment resulting from difficulties of access to the public sector, as well as increased awareness of health problems of the population that uses the private sector.

Tables 3.1, 3.2, 3.3, and 3.4 show the results of this study, with the main causes of consultation by age group [13].

An analysis of the profile of users in a referral public dermatological service in the Northeast region of Brazil, in the municipality of Fortaleza, state of Ceará, evaluated the diagnoses of dermatological appointments, at both the first appoint-

Table 3.1 The main causes of appointments, up to 15 years of age

Up to 15 years		
Diagnosis		%
1	Acne	13,9
2	Atopic dermatitis	13,7
3	Warts viral in origin	8,2
4	Superficial mycoses	6,9
5	Dermatitis: eczema/dyshidrosis	6,5
6	Viral infections/molluscum contagiosum	5,1
7	Scabies	3,6
8	Seborrheic dermatitis	3,5
9	Contact dermatitis	3,1
10	Melanocytic nevi	3,0

Source: Brazilian Society of Dermatology, 2006

Table 3.2 The main causes of appointments, from 15 to 39 years

15–39 years		
Diagnosis		%
1	Acne	26,6
2	Pigmentation disorders	9,4
3	Superficial mycoses	8,0
4	Contact dermatitis	4,0
5	Seborrheic dermatitis	3,9
6	Melanocytic nevi	3,7
7	Warts viral in origin	3,3
8	Nonscarring alopecia/telogen effluvium	3,0
9	Androgenetic alopecia	2,2
10	Dermatitis: eczema/dyshidrosis	2,2

Source: Brazilian Society of Dermatology, 2006

Table 3.3 The main causes of appointments, from 40 to 64 years

40–64 years		
Diagnosis		%
1	Pigmentation disorders	11,6
2	Superficial mycoses	10,6
3	Actinic keratosis	8,8
4	Contact dermatitis	4,2
5	Seborrheic keratosis	4,0
6	Psoriasis	3,7
7	Melanocytic nevi	3,5
8	Seborrheic dermatitis	3,4
9	Basal cell carcinoma	2,9
10	Warts viral in origin	2,4

Source: Brazilian Society of Dermatology, 2006

Table 3.4 The main causes of appointments, 65 years and over

65 ANOS e +		
Diagnosis		%
1	Actinic keratosis	17,2
2	Basal cell carcinoma	9,6
3	Superficial mycoses	8,2
4	Seborrheic keratosis	6,3
5	Epidermal thickening/xerosis	4,2
6	Squamous cell carcinoma	4,0
7	Pigmentation disorders	3,7
8	Contact dermatitis	3,5
9	Psoriasis	2,7
10	Bowen's disease	2,3

Source: Brazilian Society of Dermatology, 2006

ment and subsequent ones. Overall 9,110 consultations were carried out, and of this total 2,738 (30%) were for the diagnosis or monitoring of patients with Hansen's disease. This high frequency of Hansen's disease cases is justified because the service is a national referral center and the main center in the state for this condition (unpublished data).

Among the other 6,372 consultations, excluding data on Hansen's disease there is a relevant incidence of psoriasis (19%), BCC (12%), vitiligo (11%), and acne (10%) (Chart 3.1).

These data reflect the chronic nature of diseases such as Hansen's disease, psoriasis, and vitiligo, which require continued treatment. They also emphasize the importance of diseases such as acne and skin cancer as a public health problem.

As already noted, the nosologic user profile in dermatology depends on many variables such as gender, age, skin color, socioeconomic status, level of education, housing and hygiene, nutrition, access to health services, and the region or country where the appointment takes place, among others. In addition, in public health the demand for dermatology services is also influenced by the resolutive capacity of primary care, the efficient functioning of the system of referral, and the response to referral by specialists.
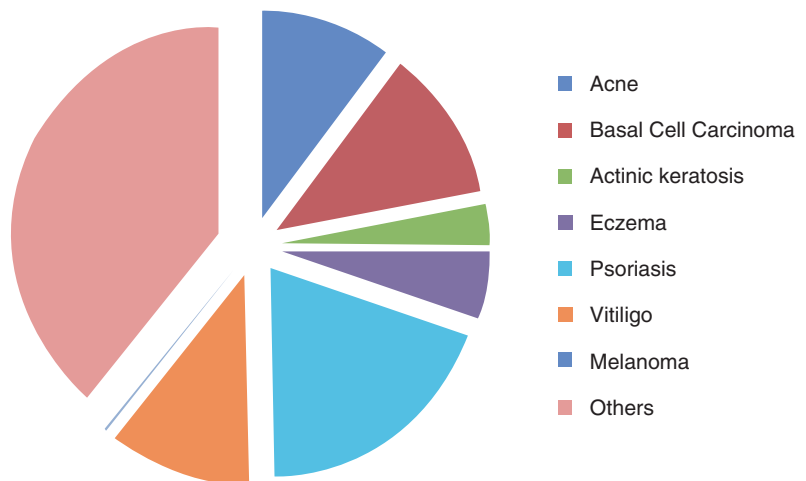

Chart 3.1 Distribution of appointments, by diagnosis (Source: Dona Libânia Center for Dermatology, 2016)

- Acne
- Basal Cell Carcinoma
- Actinic keratosis
- Eczema
- Psoriasis
- Vitiligo
- Melanoma
- Others

Perspectives

The Characteristics of a Public Health Dermatology Service

Considering the epidemiological reality in Brazil, as well as the current stage of the organization and the offer of dermatological services by the Unified Health System in the country, dermatological health actions planned and offered by a public health service in a particular area should seek to attain a resolutive capacity (human resources, equipment, pharmaceuticals and biopharmaceuticals, laboratory supplies) required to treat the following priority diseases:

- Hansen's disease
- Infectious and parasitic skin diseases of childhood
- Sexually transmitted diseases/AIDS
- Skin cancer (clinical and surgical actions)
- Allergic dermatoses
- American tegumentary leishmaniasis
- Varicose eczema and other ulcerated lesions
- Superficial and deep mycoses
- Clinical dermatoses, such as acne: psoriasis, vitiligo, collagen and genodermatoses

Therefore, the resolutive capacity of a public dermatology service is linked to the basic activities necessary for the diagnosis and treatment of such diseases. In addition, these activities should not only include medical attention but also multidisciplinary care involving nurses, physiotherapists, occupational therapists, psychologists, and pharmacists, among others. These activities are summarized in Box 3.2.

> **Box 3.2. Activities of a Public Dermatology Service**
> Medical appointments
> Nursing appointments
> Psychology appointments
> Physiotherapeutic rehabilitation activities
> Occupational therapy activities
> Phototherapy
> Dermatoscopy
> Skin biopsies

> Surgery of tumors
> Noninvasive procedures
> Simple dressings
> Debridement
> Histopathology tests
> Bacilloscopy in dermal infiltrate
> Mycology tests (direct and culture)
> Hematology and biochemistry tests
> Dispensing medicines
> Immunobiological infusion

Beyond offering care actions a dermatological health center should also be able to train primary care professionals, providing them with resolutive capacity when dealing with the most prevalent diseases in each region. Such action is essential to overcome bottlenecks and the overloading of the specialized secondary care services.

Finally, it is fundamental that these services maintain a constantly evolving research sector, whether it is epidemiological, clinical, or operational, focused on overcoming the barriers to public health in the area of dermatology.

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Impact of Preventive Campaigns in Dermatology: A Brazilian Experience

4

Maria Leide Wand-Del-Rey de Oliveira

Key Points Summary

- Concepts and practices of preventive health campaigns, health promotion, and health education
- Preventive Skin Cancer Campaign: relevant historic aspects of Brazilian Society of Dermatology initiatives
- Hansen's disease: relevant historic aspects of Brazilian government campaigns and SBD participation
- Sexually transmitted infections and acquired immunodeficiency syndrome: relevant historic aspects of Brazilian campaigns and preventive measures
- The perceived impact on epidemiological indicators of each program

Introduction

Concepts and Practices of Preventive Health Campaigns in Health Promotion and Health Education

An important lesson regarding this subject in Brazil was carried out in 1902–1906, through extensive campaigns against yellow fever, smallpox, and bubonic plague, under the management of Oswaldo Cruz [1]. It was supported by a compulsory vaccination law initiated in the then capital Rio de Janeiro, which authorized sanitary officials to enter private residences for the purpose of vaccination, in addition to other human rights violations. A consequence was a historical popular revolt, also influenced by a political period of conflict.[1]

By the end of the 1970s Bandura's social cognitive *theory of self-efficacy* introduced an explanatory model of health behavior and a guide for developing effective health promotion interventions [2]. This included four broad processes through which efficacy beliefs operate: choice behavior, effort expenditure and persistence, thought patterns, and emotional reactions. Much newer research of this theory, especially from Maibach and Murphy in 2004 [3], concluded that "no standard sets of domain specific self-efficacy items [are] applicable to all people in all situations." According to the authors, efficacy judgments not only depend on specific behaviors but also on the contexts in which they occur and the type of population involved.

Over the past decades, health mass media campaigns using mainly television, radio, handouts, and more recently the internet exemplified innovation as well as a subject for communication research [4, 5]. One derived hypothesis

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[1] Some of these procedures have been revisited because of emerging viruses.

called *the uses and gratifications* pointed out the limitations of the effects of current communication conveyed from its production source on reaching the free-thinking recipient, who selects the information according to his/her context and motivation [6]. This theoretical approach makes a connection between the mass communication process and the social context in which it occurs, highlighting the communication flow that allows for information to be shared across social media and thus increasing dissemination to more people [6].

More recently the mobile phone has played a significant role in the rapid spread of information and has started to be used in many health interventions [7]. One study concluded that interdependence exists between mass and interpersonal communication as sources of social influence and the role of media dependency in shaping media impact [8]. Another found a difference between digital natives and their older counterparts [7].

An exhaustive mass campaign evaluation performed by Backer and Rogers [9] in the State of California State in 1988 resulted in a campaign analytic framework considering 29 generalizations applied to campaign evaluations, some of them transcribed here.

Principles for what works: use multiple media, combine media and interpersonal strategies, select segment audience, use celebrities to get attention and entertainment programs to sustain attention, provide simple and clear messages, emphasize positive behavior more than negative consequences, emphasize current rewards not distant negative consequences, involve key power figures and organizations, take advantage of timing, and use formative evaluation.

To be considered in context: health care system, schools (education background), family, workplace, government, and community [9].

The same authors also highlighted the innovation proposed by campaigns termed *incremental* (short-term results) and *preventive innovation*, whose results are expected in future health campaigns. These recommendations have been adopted in the national campaign; unfortunately,

however, the understanding that health education and communication equates to the transmission from health professionals of information that aims to change the patient's behavior still persists in the health sector, including in academic institutions.

Nevertheless, comprehensive studies brought from popular educational experiences in Brazil and all Latin America contributed to clarifying the conception of health promotion, be it permanent or continuous, in service education for both health workers and the general population,[2] based on teaching/learning processes and pedagogic methodologies [10–12], as well as the experiences generated by a popular educational proposal from Paulo Freire, one principle being that education means a critical understanding of reality and dialogue [12, 13].

Bearing in mind these concepts, the first three principles mentioned [9] in addition to the context components found in different Brazilian regions show that it is vital to emphasize the importance of combining mass media propaganda with small discussion groups in each community, which is particularly applicable to the complex dermatological problems discussed in this chapter.[3]

Creative initiatives in Brazil have been produced by regional sections of the Brazilian Society of Dermatology (SBD) usually involving local universities, such as study groups of sanitary dermatology, skin disease campaigns, and educative booklets about prevalent skin diseases to be used in health education activities, mainly in schools or as a community action promoted by the Annual Brazilian Congress of Dermatologists.

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[2]From the Ottawa letter (1986) health promotion emphasized the social dimensions and the importance of five essential strategies for achieving full health: public policies, healthy environments, reinforcement of communitarian action, creation of personal abilities, and reorientation of health services.

[3]The campaign practices in Dermatology usually combine mass media propaganda and punctual patient examinations to screen for skin cancer and Hansen's disease, which includes diagnosis and treatment of general skin diseases. This could be optimized by communication and health education activities and general health promotion policy at the local level.

Also involved are health workers from basic health system care training. In 2013 one of these initiatives from São Paulo, called GRAPE (Permanent Support Group), was institutionalized by SBD to promote guidance in health education and support to people suffering skin diseases responsible for deteriorating quality of life, such as psoriasis, vitiligo, skin cancer, blistering skin diseases, alopecia areata, Hansen's disease (HD), and severe acne (www.sbd.org.br/acoes/grape-sbd/).

The proposal is to replicate this project in all Brazilian states, reinforcing an approach toward social accountability. This is to be demonstrated by the SBD commitment to provide a good quality of service and be mindful of assisting patients in maintaining a good quality of life, stimulating the civic engagement of its members through voluntary work, and pressurizing the state health sector to meet their obligations, resulting in betterment of the community.

The scope of this chapter includes the national mass media campaigns triggered by the Government specifically for infectious disease: sexually transmitted disease, mainly acquired immunodeficiency syndrome (AIDS), Hansen's Disease (HD) and degenerative diseases. The Skin Cancer Campaign (SCC) was an initiative of the SBD later implemented by the Ministry of Health (MoH).

Current Status and Perspectives

Relevant Historical Aspects of Brazilian Society of Dermatology Preventive Skin Cancer Campaign

The prominent role of the SBD in conducting a National Skin Cancer Campaign (NSCC) has been well recognized since 1999 [14]. It is worth noting that the SCC was introduced in 1988 by a Rio de Janeiro SBD section under Professor Jarbas Porto, and became a nationwide program a decade later (www.sbd.org.br/a-sbd/institucional/historia-da-sbd/) [15]. Only in 2000 was a specific formula to collect information from diagnosed cases of skin cancer implemented and

welcomed by all Dermatology services [16]. The first historical series of data consolidation carried out in 2005 showed that of the 205,869 dermatological examinations done in this period, 17,980 (8.7%) cases of skin cancer were diagnosed (13,194 basal cell carcinomas, 2,482 squamous cell carcinomas, 1,057 melanomas, and 1,247 other neoplasms). The ratio between sexes was 1.7, and unprotected sun exposure was not yet perceived as an important health risk [17].

Currently the annual SCC is an institutionalized activity not only comprising the spreading of information about the most prevalent and serious skin cancers, but also giving specialized dermatological assistance to spontaneous and stimulated demand via thousands of voluntary dermatologists around the country as a component of the National Program of Skin Cancer Control. The latest statistics from annual campaigns by the Dermatology Service can be found on the SBD website: www.sbd.org.br/acoes/programa-nacional-de-combate-ao-cancer-da-pele/.

This potent program received the Guinness Book certification in 17 June 2010 as the biggest medical campaign performed in 1 day, called *Day C* (www.sbd.org.br/acoes/dia-de-combate-ao-cancer-da-pele/).

In general, these events took place on the last Saturday of November and involved hundreds of health units in health education activities, assisting all suspected cases of skin cancer as well as other skin diseases, with those diagnosed referred to be treated. Thus, the waiting list for this form of medical assistance was reduced alongside increased job training for young dermatologists and primary health care workers. At local level the assistance is usually provided by University Dermatology Sectors in each state, with great participation of dermatology residents, supervised by their professors [18].

Since 2009 the National Program of Skin Cancer (NPSC) has included one roaming activity, The Skin Cancer Combat Truck, which has been covering the entire Brazilian coast. This activity was launched in Rio de Janeiro city in December 2009 and is called *Orange December.* This mobile health attendance vehicle has already traveled 69,000 km, offering attendance to about

16,000 persons living in 56 small cities in 22 states, where 1,500 skin cancer cases were diagnosed (www.sbd.org.br/acoes/tour-de-combate-cancer-da-pele/) [19].

The Department of Oncology of the SBD is responsible for all planning and execution processes receiving technical support from the Brazilian Society of Surgical Dermatology. It involves 23 regional SBD sections plus the country's capital city in 24 metropolitan cities (23 out of 27 states) and also in some municipalities of more populous states. Of course the voluntary work of dermatologists should also be acknowledged.

Also worthy of mention is the study group of Melanoma-GBM (www.gbm.org.br), which has spread updated information to associated dermatologists since 1998 through its delivered bulletin and scientific national and international meetings, with prolific scientific information on this subject provided by its dermatologist and pathologist members in collaboration with the NPSC activities [20]. All societies and group studies linked to SBD exhibit skin cancer prevention information on their web sites. A quiz test of skin cancer risk is available on the SBD site with guidance in accordance with the user's results (www.sbd.org.br/informacoes/sobre-o-cancer-da-pele/calcule-seu-risco/).

On the web pages of the Brazilian MoH, the cancer institute holds national data of all forms of cancers alongside useful technical and basic information to prevent skin cancer (http://www.inca.gov.br).

The Impact Perceived by SCC on Epidemiological Indicators and Perspectives

The Brazilian MoH estimated for 2016 175,760 cases of nonmelanoma skin cancers (NMSC): 80,850 cases for men and 94,910 for women. This is the most frequent cancer in men in the Southern, Central Western, and Southeastern Brazilian regions while in the North it is ranked second. It is also the most common cancer in women from regions in the Southeast, Central West, South, and Northeast. NMSC has a low death rate in contrast to malignant melanoma

(MM), which is estimated to produce 3,000 new cases in men and 2,670 cases in women in 2016 and an incidence rate of 3.03 per 100,000 inhabitants, more prevalent in the South (http://www.inca.gov.br/estimativa/2016/) [21]. The comparison of these general data with the same MoH estimate for 2005 indicates a low impact on preventive measures against skin cancer incidence, around 60 per 100,000 inhabitants for NMSC and 3.04 per 100,000 for MM [22].

Research indicates that solar radiation is not the sole influential factor in the genesis of cancer, as skin cancer does manifest in the absence of solar elastosis [23]. Despite the controversies regarding the association of skin cancer with other risk factors besides solar exposition of skin, the campaign target is to increase awareness of disease prevention through protection from ultraviolet (UV) radiation. This consists in information on early signs and symptoms of each kind of skin cancer and its spread, and recommends adoption of new practices or modification in job routines, activities, sport, and so forth [24, 25].

Some studies to assess the knowledge about skin cancer prevention and its association with sun exposure and photoprotection were undertaken mainly in South and Southeastern Brazil where there is a predominance of European ancestries. From a case-control study of 206 melanoma patients in Porto Alegre conducted over a 3-year period from 1995 to 1998, Bakos et al. concluded that light prototypes were more prone to the development of cutaneous melanoma and that the most important associated risk factor was frequent sunburn episodes [26]. In a more recent study the same author proposed a risk score of MM for a Brazilian sample, concluding that in the population studied the best predictive variable for the risk of MM was hair color, in addition to freckles, sunburn episodes, and skin and eye color [24].

In the same city, Benvenuto-Andrade et al. interviewed 724 students about known effects of UV radiation, opinions about tanning, total time of sun exposure per day, photoprotection, and activities in the sun. The results showed that about 90% were aware of the association between sun exposure and skin cancer. The main

source of information was mass media, but only 47% reported sunscreen use in summer and only 3% reported using sunscreen during winter. The study conclusion was that although campaigns disseminated information they were not successful in changing the sun exposure habits of teenagers [27]. Fabris et al. interviewed gym members in a cross-sectional descriptive study utilizing a self-administered questionnaire during 2009 in Santa Catarina state. From 317 questionnaires studied, 94.3% of the participants reported that they had heard about the risks of sun exposure, mostly in terms of skin cancer risk (80.8%), but only 74.1%, especially women, reported using some form of sun-protective measure. A higher frequency of photoexposure was observed in individuals younger than 40 years, and the risk of daily exposure was more frequent in people between 20 and 40 years of age. The conclusion was that these individuals were aware of the risks of excessive sun exposure and skin cancer prevention, but had not yet incorporated appropriate sun-protection measures into their daily habits [28].

One avenue of research intends to correlate audience patterns on the web pages of a Brazilian MoH cancer institute (http://www.inca.gov.br), observing the interest patterns measured by the preferred topics consulted by whomever logs it. The authors monitored the skin cancer site for 24 consecutive months using a commercial software package to document electronic records analysis (log files) of all visitor traffic. Variables of interest included number of visits, time spent on each visit, and the monthly return rate to six selected pages (three relating to cancer as a disease and three to prevention measures). The authors observed peak audiences in periods during the nationwide campaigns. The topics of most interest were concentrated on pages regarding cancer diagnostics and treatment technology. Pages on preventive measures were less visited during the campaigns, and their audience varied little over the 24 months [29].

While no impact is observed in NMSC and or MM frequency, some regional and national investigations did start to show a decrease in advanced forms of MM measured by specific markers.

These data have been appropriately applied, and the improvement in observed 5-year survival and decrease in mortality as a result of early diagnosis probably is related to the SBD's continuous case-finding campaigns and primary health care implementation in Brazil. It is well known that a person with MM can be cured if diagnosed in a phase classified as 1A, whereby the success rate is about 95–97% [30]. A study from Rio Grande do Sul state focused on histopathological criteria established by GBM in a sample of 328 cases between January 1, 2000 and January 15, 2005. Although all cases belonged to a tertiary care hospital, there was a predominance (63.1%) of melanomas considered thin (Breslow thickness ≤1 mm), in comparison with a previous and similar study in the 1990s that presented 2.15% of melanomas in situ and 31.5% with Breslow thickness ≤1.5 mm. The conclusion was that the profile of melanoma cases evaluated in a tertiary referral hospital appears to be changing, with a tendency toward earlier diagnosis [31]. In the Southern region town of Florianopolis, 496 reports of two pathology laboratories on 432 patients with a pathological diagnosis of melanoma were analyzed in a 6-year period with a protocol based on the GBM questionnaire. As a result, the main histopathological profile was superficial spreading, invasive, 1.25-mm Breslow thickness, cutaneous melanomas with inflammatory infiltrate and free margin [32].

Action research performed by one non governmental organization (NGO) carried out 17,857 consultations with a total of 2,012 (11.2%) cases of skin cancer diagnosed from 2004 to 2017 in the interior of São Paulo state. The predominant histological type reported was BCC (81.6%), followed by basosquamous cell carcinoma, but no stage-III and -IV melanomas were found [33].

Regarding the incidence and mortality rate of cutaneous melanoma, a study in the city of Jaú, São Paulo, from 1996 to 2011 presented the data of 162 new cases provided by the local Population-Based Cancer Registry and Mortality Information System of the MoH (SIM). The average incidence for females was 5.1 per 100,000 and 4.8 per 100,000 for males, both showing stability during the period. The

same behavior was observed regarding the mortality rate while an increased incidence in stage 0 and a decrease in stages I and II was confirmed, leading to the conclusion that early diagnosis of cutaneous melanoma has a possible relation to the local program of continuous prevention, together with the NPSC of SBD [34]. A survival, but descriptive clinical and histopathological, study from Santa Catarina state analyzed 83 cases of primary cutaneous melanoma diagnosed in the period 2002–2003 followed for 8 years, and correlated its survival with the tumor phase: 27% presenting with stage 0 and all remaining alive in the monitored period: from 20,5% in stage I, one died (93.8% survival). From 33% in stage II and 19.2% in stage III, the survival was the same, 33.3%, and all patients in stage III died in the same year of their diagnosis. The average survival period on this casuistic was 56.7 months and the mortality rate was 7.0%. The author's conclusion was that ulceration and the final staging were statistically significant factors [35].

One epidemiological study performed in 2010 at an oncology center in Rio de Janeiro aims to evaluate aspects related to temporal trends in mortality of melanoma in the Brazilian population. The mortality data were obtained from SIM, and two groups were analyzed: one during 1997–2001 and another during 2002–2006. A total of 19,218 melanoma-associated deaths were reported in Brazil, 10,899 among males and 8,309 in females, most of them occurring in whites older than 50 years. The mortality ratio comparing South and North regions was 7 in 2005. An increase in mortality of 1.1% per year was observed in the period between 1980 and 2005 with different rates according to sex, age groups, and geographical regions. However, when only the last 10 years were analyzed a decrease of 0.6% per year in increased magnitude of mortality for the whole country was observed. Among older people (>70 years) it was 3.0% per year and among females, 1.6% per year [2] in the regions South and Central West [36, 37]. The same author investigated the role of socioeconomic factors in the evolution of melanoma in a retrospective

study of 1,083 incidental patients with melanoma treated in an oncology center in Rio de Janeiro during the period 1997–2004. From 1,083 patients with primary melanoma of the skin, 58.1% had low school attendance, and 5-year survival for the entire group was 67.0%. Males had worse survival and a protective effect was found for whites, higher educational level, and upper limb lesions. A higher risk of death was observed for patients with nodular melanoma, acrolentiginous melanoma lesions in the soles and palms, and increasing age. In conclusion, socioeconomic status as measured by educational level represented an important factor related to clinical evolution of melanoma in the cohort studied [38].

Despite this social inequity, diverse initiatives in the field, such as the Skin Cancer Combat Truck [19] and annual campaigns from SBD, the Mobile Unit (MU) of Barretos Cancer Hospital [33], and GBM actions [39], have helped to improve the inadequate public health system regarding skin cancer screening and treatment.

In conclusion, the remarkable efforts of SBD and its members should continue to emphasize robust research addressing the monitoring of skin cancer trends, as well as promoting and reinforcing sun-exposure awareness through preventive actions targeting high-risk individuals. Epidemiological studies to identify the demographic characteristics of high-risk patients in different regions will be useful to guide local preventive plans.

Relevant Historical Aspects of Brazilian Government Campaigns of Hansen's Disease

The "World Leprosy Day" at the end of January was created by Follereau in 1954, and was recognized by the International Leprosy Association (ILA) in Europe, which coordinated a media campaign to spread information about the disease. Nonetheless, the main objective was to raise funds to support leprosy projects in endemic countries (http://leprosyhistory.org/). Regrettably it was included in the agenda of

official Programs of HD in Brazil, at national and state levels, only at the end of the 1980s.[4]

Since the middle of the 1970s the term *leprosy* and all correlate adjectives were replaced by the term Hansen's disease (HD) by the MoH of Brazil after pressure from SBD and the Brazilian Leprologists Society (SBH) [40]. It was instigated by its member Rotberg, who adopted this term when in charge of the Hansen's Disease Program of Secretariat of Health, São Paulo [41]. However, only in 1995 was it legally banned under pressure from the Movement for the Reintegration of Hansen's Disease Patients (Morhan) [42], and the first mass media campaign introducing HD concepts and its images only took place in 1986/1987 [43]. This campaign included three short films for TV, jingles with regional rhymes, outdoors and indoor posters, and handouts. Its contents were deeply discussed and many local activities and health professional training sessions were conducted all over Brazil to implement a new treatment for HD (*poliquimioterapy*; PQT). The campaign proposal was to be maintained yearly for 5 years; nevertheless this regularity was not observed, despite other nationwide campaigns carried out from the MoH since then [44]. One survey performed in 1988 (1 year after the HD campaign) questioned 1,797 persons about MoH campaign memories. Among 24 diseases, HD was mentioned in ninth position.[5]

In 2001 evaluation research was conducted in four metropolitan regions of Rio de Janeiro in order to understand whether the popularization of scientific notions of HD had been assimilated by 800 interviewed housewives. The results showed that 436 (54%) promptly expressed their association with the word Hansen's disease/*hanseníase* while 358 (45.1%) expressed association only to leprosy. It was possible to infer that the common sense of HD was in transition, linked to skin patches and curable disease, while leprosy was linked to incurable dog disease.[6] The interviewees were 42 years old on average, and the HD knowledge was positively associated with education level [45].

It has been noted that since the introduction of the neologism *hanseníase*, also adopted by the communication mass media, all official information directed to health professionals, but mainly for the general population, omits the link with the term leprosy. The collective memory of leprosy in that population is mostly oral and mainly influenced by individuals' social networks. Based on the theory of social representation, we may conclude that HD is part of a process of modernization of common thinking, anchored in the traditional representation of leprosy [45]. It is well known by health workers in Brazil that even patients under treatment for HD were sometimes doubtful as to whether their illness was leprosy or not [46]. It may be that 30 years is not a sufficient time to consolidate a social representation of HD. Furthermore, the investment in social marketing to make the new terminology better known started a full decade after the neologism was implemented.

This first campaign of HD by the end of the 1980s prioritized the information of a cure,[7] and one finding from our research in the beginning of 2000 shows the absence of knowledge of skin hypoesthesia (numbness) as an HD symptom. This result was discussed and focused upon in the following campaign by MoH and BBC/Novartis in 2003. This campaign publicized loss of sensation of the skin in different situations with the objective of retaining this information (http://www.comminit.com/content/leprosy-awareness-campaign).[8]

In addition to the first national TV campaign, a great variety of learning materials for community agents, handout materials, and radio jingles produced in all regions by 27 states and some

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[4]Observation from this author.

[5]Report from the survey "Life Style of Brazilian Population (LPM)" requested from the National Secretary of Chronic and Degenerative Diseases of MoH, (988) (author repository).

[6]This belief is mainly present in the peripheral area of metropolitan city Rio de Janeiro and it can be seen in a video at http://hanseniaseufrj.blogspot.com.br/2014/09/trecho-extraido-da-videoteca-do-nutes.html.

[7](a) Let's stop this spot in Brazil; (b) Hanseníase can be cured.

[8]BBC Campaign run in February 2003.

municipalities has been spreading basic knowledge about HD around Brazil. The same strategy was repeated by a BBC campaign in 2003.

Usually the campaign did not comprise active "case finding" of HD before the end of the 1990s, when the World Health Organization (WHO) launched the strategies called LEC (Leprosy Elimination Campaign) and Special Projects to Eliminate Leprosy (SAPEL) [47]. The former is an initiative aimed at detecting "leprosy cases with consequences," which means advanced and undetected cases by passive Primary Health Care (PHC) assistance. SAPEL is an initiative focused on the neglected population, some of whom live in difficult-to-access areas or situations. Both target the hidden prevalence of the disease. The regional offices of WHO selected projects and some resources were addressed, mainly to SAPEL.

In Brazil the first experience of WHO/LEC was performed in Rio de Janeiro municipality with an HD campaign combined with a poliomyelitis vaccination campaign in 1997, involving all dermatologists from the municipal health network [48]. In 1998 the National HD Program planned to repeat this strategy all over the country, but unfortunately the MoH was afraid that it could jeopardize the polio campaign and did not officially support it. Despite this, 390 municipalities performed this campaign in 20 states and 2,400 new HD cases were diagnosed in a single day (5% of yearly estimated detection) [49]. Rio de Janeiro municipality maintained this strategy continuously for more than a decade, and currently many municipalities around the country carry out active case-finding campaigns. In addition to the *World Day,* some states also defined a *Hanseníase Day*, considering that January is not an appropriate month to hold this campaign in Brazil.

The Brazilian SBD even supports the national and local campaigns of HD, but only assumed its own initiatives in 2005[9] when municipal campaigns were launched involving its regional sec-

tions from the most endemic states [50]. This proposal included distributing two posters to be displayed at health units across the country, one of them focusing on stopping HD in children and emphasizing the participation of a dermatologist in this kind of activity as essential to increasing the diagnostic accuracy of HD; the other focused on resolution of other dermatoses and PHC training.[10] It is worth mentioning that one of the targets of the current strategic WHO plan for 2016–2020 is to achieve zero cases of leprosy in children [51].

Since then the SBD has been participating in these campaigns of the National Program of HD, in addition to municipal-level participation of dermatologists, residents, and medical students. As well as in one roaming activity, utilizing a truck to diagnose HD, supported by Novartis Foundation. Such strategies demands a strong integration of leprosy managers and universities in each state, thus allowing new learning and teaching opportunities. It certainly will also contribute to early diagnosis of HD, which is still a challenge for many Brazilian municipalities.

The Impact Perceived by HD Campaigns on Epidemiological Indicators and Perspectives

The first national mass media campaign of HD of the National Division of Sanitary Dermatology of (DNDS), MoH, increased by 31.5% (almost 7,000) the number of new cases in 1987 [43]. In one national survey of private dermatological clinics around the country by ordinary mail, 99% of recipients returned the forms which collected the following information: 770 persons referred to the mass media campaign as a motivation to go to the clinic while 501 presented clinical suspicion or at least a differential diagnosis of HD, 291 of which were confirmed.[11] The existence of this hidden prevalence is supported by a trend analysis which shows an increased tendency of the disease in four Brazilian regions, excluding only the South [52].

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[9]SBD president and vice president (Sinésio Talhari and Gerson Penna: 2005–2006), and the HD Department consisted of Maurício Nobre (NE), Fatima Maroja (NO), Francisca Estrela, Luna Azulay, and myself.

[10]This proposal received support from the ILEP member Netherlands Leprosy Relief.

[11]Report from then the National Division of Dermatology. Document copy of this author's repository.

Nevertheless, the best indicators of this punctual strategy measurement are the proportion of disability grade in the total number of new cases diagnosed as well as its clinical form and disease features, which indicate early diagnoses or not. The impact could be measured in the longer term by reduction of the number of cases, especially the pediatric rate [53]. As mentioned earlier, the first evaluation of LEC strategy was performed in Rio de Janeiro city in 1996 by combining HD and anti-polio vaccination. The mass media campaign carried out from July to September and the intensive examination on 17 August increased the health unit locations for HD diagnosis and treatment from 28 to 70 by utilizing the vaccination venues. From the 2,511 persons assisted, 52 new cases were confirmed, 30.8% presenting an indeterminate form of the disease [48].

Other good examples exist in Acre state, which was the most endemic state of Brazil 30 years ago and managed to produce a well-conducted and continuous policy of performing active case finding across the rivers in the Amazon forest. After the municipalization, the coordinator of the Program of State Secretariat of Health invited the university service to expand the campaign to all municipalities to verify whether the decreased detection rate in passive diagnosis at PHC was true. The first campaign in 2001[12] was preceded by population domiciliary visit screening carried out by trained community agents of the Health Family Program in the two biggest cities. Of the 11,720 persons examined, 2,881 (24.58%) presented skin problems and were referred to the campaign; 11,638 (91.56%) were examined and 53 new cases of HD were diagnosed (2.01%). The early diagnosis was corroborated by the low disability grade (96.22% = 0, only one presenting grade II) and only four cases (7.5%) showing positive smears. Despite this, the number of HD cases diagnosed in this campaign was higher than the total number of new cases

during the entire previous year in the same municipalities. In addition, 5% of new cases in the previous year presented grade II disability. It could thus be inferred that there were few undetected cases by PHC [54].

The second campaign was included in the SBD Project of 2006. A task force was organized with the participation of residents of Dermatology from Rio de Janeiro and Espírito Santo states, and medical students and health professionals from Acre, supervised by professors from federal universities of Rio de Janeiro. The team was also composed of nurses, physiotherapists, and one mobile laboratory for skin smears from the State HD Program. It was not preceded by a screening process but by a mass media campaign (radio, TV, posters, handouts) covering all Acre state, besides scheduled examination in the municipal reference unit of each municipality in the 20 cities visited. In 2 weeks 10,214 examinations of referred persons was done and 318 new cases of HD were confirmed (3.11%), 0.37% of whom [32] were younger than 15 years. Only 2.20% of cases presented grade II disability and only 8.17% had positive smears. The small difference found in comparison with 2001 results could be related to the remote municipalities visited and the lesser supervision in small communities.

The TV campaign in 2008 focused on contacts surveillance; for example, a mother suffering HD alongside her children, publicizing that she must take care of her family. A more recent campaign includes HD among the neglected diseases, related to the new policy of MoH that emphasizes the persistence of clusters of the disease located in impoverished areas (http://bvsms.saude.gov.br/bvs/publicacoes/plano_integrado_acoes_estrategicas_2011_2015.pdf) [55].

Since 2011 the new policy of the Brazilian MoH for HD is defined as an "Integrated Strategic Action Plan for elimination of leprosy, lymphatic filariasis, onchocerciasis, schistosomiasis, trachoma as a cause of blindness and control of soil-transmitted helminthases (STH)" [55]. It includes a case-finding campaign aimed at 9.2 million school-aged children in 800 municipalities in 27 states. It has also allowed the early detection of leprosy cases and the reduction of morbidity

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[12] The operational research "The social role of dermatologists: importance of early diagnosis of leprosy and prevalent skin diseases" received the award for the best community operational research from the Dermatology Residents Forum at the 56th Brazilian Congress.

caused by STH, since these parasites have a high impact on the growth and development of children under 15 years old. It is for this reason that deworming has focused mainly on this age group.

The strategy for this mobilization is for health professionals from the MoH to administer albendazole, backed by the state and the municipalities in coordination with teachers in schools. For the case finding of HD, teachers have been collecting information regarding the presence of possible signs and symptoms of this disease in students. Suspected cases are referred to the family-health teams for diagnostic confirmation while the complicated cases are referred to university hospitals as agreed by SBD/MoH and Dermatology Services.

Despite a recent reduction in detection rates of HD in Brazil, there is still active transmission and late diagnosis in many clusters located mainly in the Northeast, Center West, and Northern regions. Further specific actions must be maintained to improve early case detection and prompt treatment with the aim of reducing the disease burden in the population, considering existing social inequities in the country [56].

In addition to the impact related to endemic traits, it must be mentioned that the stigma and self-prejudice related to leprosy and compulsory hospitalization period [57, 58] filtered through to HD and consequently impaired the quality of life of its carriers, even in the absence of deformities [59].

Nonetheless, fears of exclusion are mainly associated with the physical disfigurements, development of disabilities, ability to work, contagiousness, and pain in many situations found in Brazilian studies [60–62]. This has a negative influence on the patients' treatment management and their household contacts surveillance. Therefore, all efforts addressing counseling and community-based rehabilitation to the patients and their families follow the Global Leprosy Strategy 2016–2020 [51]. This latest guideline of WHO, *Accelerating Towards a Leprosy-Free World*, includes partnership promotion "with state and non-state actors and promote intersectoral collaboration and partnerships at the international level and within countries." In Brazil the

official involvement of SBD in the MoH policy is required to guarantee best practice in early diagnosis through the integration of dermatologists in a multidisciplinary team of health workers [63].

Sexually Transmitted Infections (STIs) and AIDS: Relevant Historic Aspects of Brazilian Campaigns

Since the eighteenth century many authors, including Brazilian dermatologists [64], have encouraged medical diligence to raise governmental attention to the consequences of syphilis for humanity. The first official health policy involving dermatology was called *Inspectoria de Profilaxia da Lepra e Doenças Venéreas,* which was first formulated in 1920 and was coordinated by Eduardo Rabello [65, 66]. The internalization of assistance and preventive measures was planned through the Countryside Prophylaxis Services, and one recommendation was for centers of venereal disease for regional assistance and training [64, 66].

However, this policy did not reach all Brazilian states and was not maintained or consolidated as exemplified in the historical register of São Sebastião Hospital, also called "*Asilo das Madalenas* [67]" in Pará State, which was closed because of both local society pressure and the existence of many other health problems. However, in the then capital city, Rio de Janeiro, one good example of a private initiative was the Gafree Guinle Foundation, inaugurated in 1929 and also following the national policy [66].

After the advent of penicillin for syphilis indications in 1943, and later new antibiotics discoveries, the syphilis scourge and other STIs could be faced, despite being neglected as a public health problem [68–70]. The period of strong sanitary policy led to a strategy to control the sexual market throughout the urban spaces, creating segregated prostitution zones monitored by judiciary intervention as well as joint action of the public health department and the police. The main action was the compulsory and periodic examination of the prostitutes who, if in good health, received a green card granting permission

to work in those spaces. This was a well-documented official measure to protect men who frequented such areas, for example in Santa Catarina state [71].

The two decades of 1960 and 1970 witnessed expansion of STI related to strong behavioral changes linked to young people's freedom, sexual liberation, unsafe injection of drugs, migration to the metropolis, and globalization. Viral diseases such as human papilloma virus (HPV), hepatitis B virus (HBV), herpes simplex virus (HSV), and chlamydia trachomatis were linked to the classical STI group [72, 73]. Even though these diseases were not considered a prioritized public health problem at this time, the high level of hospital assistance rather than the health needs of the population constituted the central focus of Brazilian public health. The MoH function was restricted to formulated guidelines [74, 75] and few university services offered reference services for assistance, training, and research.[13]

Later, a new tragedy emerged in this group of diseases with the advent of AIDS in 1981 [76]. The available technology, magnitude, and transcendence of AIDS generated within a short time not only knowledge of its physiopathogenesis but also a new generation of medications to treat other diseases [77, 78].

Regarding health promotion, we could infer that AIDS provoked a well-documented revolution, obliging society to open the discussion and redefine knowledge of issues considered taboo up to this era, such as homosexuality, sexual activity out of wedlock, the ever present sexual market, and the modern ways to protect human foibles [79–81].

It is well known that despite all the suffering conveyed, in Brazil AIDS brought second-ary benefits such as blood supply, hepatitis, and tuberculosis program controls [78]. The accumulated experience with a nationwide control plan from the MoH developed with the civil society is also a model for general health policies [78, 82]. Worthy of mention is the new policy to confront and protect injecting drug users, including the harm reduction strategy, started in 1989 from one pilot and successful project in Santos in São Paulo State, adopted by the government to support the needle exchange program and later on to be included among the national program strategies [83].

After those first known cases from São Paulo[14] the disease spread promptly over the course of the next decade [78, 84, 85]. Fortunately, a relatively early and well-formulated response to the epidemic emerged from São Paulo, which was utilized over the long term as an important model for Brazilian states and even MoH plans [86, 87]. The earliest published cases of AIDS concentrated in São Paulo were followed by the emergence of powerful gay organizations in Brazil and the regrettable infection of numerous hemophilic patients, which presented an opportune moment to apply political pressure on the MoH to respond and confront the emerging epidemic [87].

By 1985 the MoH formalized the National AIDS actions in the Dermatology sector (DNDS) with the first and fragile guideline for the State Secretariat of Health, and began the mass media initiatives, which in fact were considered weak and unsuitable and usually not relevant.[15]

From 1986 to 1992, along with the political and administrative changes in a wider countrywide context, sanitary reform created the Unified Health System (SUS), and a robust nationwide

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[13] Observations from this author's experience: (a) In the beginning of the 1970s the State Secretariat of Health of Espírito Santo state supported a reference center for diagnosis and treatment of DST, offering a field for medical student practices .(b) In the early 1980s The DNDS/MoH started offering training on Sanitary Dermatology and the trainees went to Porto Alegre in order to have practice. (c) At the same time in Rio de Janeiro city the State Blood Storage notified all blood donors who tested positive for syphilis, but there was no subsequent surveillance action.

[14] The first case of AIDS identified and released in a scientific society in Brazil comes from São Paulo, presented by Valéria Petri at the Brazilian Dermatology Society (SBD) Congress in 1982, Rio de Janeiro.

[15] I received it in Rio de Janeiro as state coordinator of Sanitary Dermatology. Also, DNDS triggered one TV campaign with Sócrates (football player) and provided an international course in 1985 for Aguinaldo Gonçalves, in charge of the National Programe, Paulo Teixeira from SP, the coordinator of DF (Brasilia) and I from RJ state. Paulo Teixeira, one technician from DF, one from MoH, and one from Rio de Janeiro.

program of AIDS and STI control was created [86–89]. This started in February 1986 with a national meeting of DNDS when two workgroups to formulate action plans for both AIDS and HD were set up. Both were officially published in April 1986 with a Disease National Advisory Committee assigned to each. The two immediate activities were to create a form and information system for AIDS case notification (manual at the time) and to start formulating a nationwide campaign.[16] The National Program for AIDS and STI Control was created out of the Dermatology sector at the end of 1986, receiving internal support from the National Institute of Medical Assistance and Social Security, and was implemented with foreign resources from the WHO and the Pan American Health Organization, before the loan agreement between the Brazilian government and the World Bank in 1992 [90]. This become an internationally referenced public health intervention plan, allowed to sponsor many civil society organization projects not only from the groups initially linked to the program but also from different parties such as sex workers, feminism groups, health promotion, and others [91, 92]. By 1992 the high number of human immunodeficiency virus (HIV) carriers and diversified profiles of AIDS patients oriented the guideline to decentralize diagnosis and treatment from reference centers to PHC of SUS [91]. As a result of the first impact on the endemics indicators, by the

end of 2000 the protagonist role of the Brazilian program was recognized worldwide, and in 2001 the Brazilian government obtained free universal access to antiretroviral drugs [93–95]. Currently the Hepatitis Combat is integrated into a larger AIDS Program and there is a discussion about the possibility to join the Tuberculosis Program in the Department of DST-AIDS and Viral Hepatitis of MoH.[17]

With AIDS renowned as the most devastating disease humankind has ever faced, the Joint United Nations Program on HIV/AIDS (UNAIDS) formed by 11 cosponsors and the Global Fund to Fight AIDS, Tuberculosis and Malaria demonstrate how it is possible to build a universal and powerful intervention plan to fight pandemics (http://www.unaids.org).

Health education and health promotion were great beneficiaries of these efforts. Many research studies, learning materials, and campaigns from the government and private organizations were triggered to deal with complex and dynamic endemics [96]. In the previously mentioned inquiry of 1,797 Brazilians about their memories of MoH campaigns performed in 1988 (1 year after the first strong AIDS campaign), AIDS was rated in second position among 24 disease campaigns.

All issues and contents of the official campaigns for STI, mainly AIDS, since 1998,[18] not only from MoH but also including UNAIDS initiatives, can be found on the web site of the National Program of MoH (http://www.aids.gov.br/campanhas). The creative and positive single-mindedness of these campaigns is perceptible, principally if compared with other countries and in contrast to the beginning when mass media connected AIDS with death and terror [97, 98]. The focus on human rights, self-esteem, disease information, and stimulus for preservative use is in agreement with the concept of vulnerability reduction, which replaced the notion of preliminary risk conception. In addition to MoH campaigns, many other Brazilian institutions also elicited its own campaigns, such as Globo televi-

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[16]While in charge of DNDS this author first invited Dr. Paulo Teixeira to coordinate the workgroup and then Professor Lair Guerra de Macedo who was working in STI in the Women Program/MoH, to be responsible for AIDS/SDI; Dr. Miriam Franchini to be responsible for STI training; and Dr. Jair Ferreira to take part in both committees as epidemiologist. Many difficulties were encountered at the beginning, when MoH had a very poor infrastructure and budget (before SUS) and had just started working with civil organizations through DNDS (MORHAN, GAPA, ABIA, GGB, and hemophilia associations). Also important was the support from SESP Foundation Network training an all-doctors team coordinated by Dr. Pedro Chequer. Also the recognition of STI state referral centers for training in Porto Alegre (the film Love without pain – Gerbase/RGS), the Laboratory in Brasilia (Miriam Franchini), and Alfredo da Matta Reference Center (Adele Benzakem, Sinesio Talhari and JCG Sardinha).

[17]Oral information from health workers' meeting.

[18]Missed campaign from the first decade.

sion in the early 1990s and the National Bishops Conference of the Catholic Church in 2008 and 2012, despite conflicts regarding extramarital sexual activity [97–99].

During the FIFA World Cup in Brazil in 2014, UNAIDS drove the kick-off of the *Protect the Goal* world tour campaign first launched at the 2010 FIFA World Cup in South Africa to raise awareness around HIV prevention and to encourage young people to become actively involved in both the national and global response to HIV (http://www.unaids. org/en/resources/presscentre/pressreleaseand- statementarchive/2014/march/20140305 prptg) [98].

Alongside all mass media campaigns for TV and radio, there are a great number of university health and social workers performing participative research into community groups as well as many factories involved in educative experiences with its workers in each state of Brazil, as a result of NGO participation in the national policy [100, 101]. However, achieving the ideal scenario to provide early diagnosis and treatment facilities for STI patients and their partners is still a challenge [102].

The Perceived Impact on Epidemiological Indicators of STI and AIDS, and Perspectives

The special session on AIDS/HIV of the United Nations General Assembly in June 2001 concluded that there was an emerging rise in infection rates from high-income countries and absence of control in some other low-income countries, mainly in Africa, despite reasonable achievements as a result of 20 years of intense response to the disease. What is propelling this is well known: unsafe sex, reflected in STI outbreaks, and widespread injecting drug use of epidemic proportion shifting toward deprived communities. The final resolution—*stronger commitment*—was directed to develop multisector strategies to address the impact of the HIV/AIDS epidemic at the individual, family, and national levels of all endemic countries [103].

In Brazil, the increase in syphilis[19] in the last decades was considered a sentinel to intensify the surveillance for all STIs [104]. Since 1986 congenital syphilis has been included in a compulsory list of notifiable diseases, and the current recommendation is two syphilis tests during pregnancy and one at delivery, in addition to other official programs for maternal and neonatal care [105–107]. However, studies still show that women are not tested during pregnancy or at delivery. The WHO elimination target for congenital syphilis is <0.5 cases per 1,000 neonates up to 2015 [108], but despite a notable reduction over the last years the recent epidemiological and operational information demonstrates some difficulty in achieving this target in Brazil, where it was 4.7 per 1,000 neonates in 2014 [109]. A wide difference between regions was observed, but all patients not only maintained high levels of positivity rates for syphilis in pregnant women, but also a treatment gap for their partners [109]. This is justified by the weaknesses of prenatal care in the Brazilian health system, probably in addition to a penicillin shortage in 2015 creating a risk factor for syphilis infection during pregnancy. Recently, the Brazilian Medical Council circulated a recommendation to commit doctors to request standard examinations for STI [110].

The commitment of Latin American and Caribbean countries to reduce the vertical HIV transmission was to achieve a target for 2015 of ≤2%, or incidence rate of 0.3 cases per 1,000 neonates [108]. In 2006 a national prevalence study showed that even in those who were pregnant and were submitted to adequate prenatal tests, considering the moment and the number of tests done, absence of HIV testing was observed in 22.5% [104]. Although the detection rate in children (<5 years old) as a proxy indicator to monitor the vertical transmission of AIDS also underwent a significant decrease in Brazil, in the North region it increased from 2.9 to 4.4 per 100,000 inhabitants [109].

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[19]Despite only congenital syphilis being notified, there is a consensus about diagnosis increasing in the routine consultancies of Brazilian dermatologists.

Nevertheless, some questions may arise concerning the increase in AIDS/HIV and syphilis, possibly influenced by factors such as notification improvement, interdiction to sell antibiotics in pharmacies without medical prescription,[20] notification and treatment of HIV carriers, and the use of databank linkage analysis in the AIDS Program.

The characteristics of STIs, and especially AIDS, currently affecting different vulnerable and marginalized groups in developing countries are reasonably well documented [103]. Their dynamic processes imply effective monitoring to guide regional and local action plans. An example concerns the observed increased prevalence in the elderly, which may be related to longer sex lives in persons who by and large are not users of condoms [111–113].

The men/women and hetero-/homosexual predominance in these groups has been subject to change. Dealing with injectable drug addiction requires integration with social policy areas in order to formulate a harm-reduction project for each specific situation [114].

The latest national inquiry of knowledge, attitudes, and practices related to STI/AIDS (2008) in a randomized sample of the population in the age group between 15 and 64 years from all Brazilian regions showed that sexual initiation of one-fourth of individuals was before 15 years old and in those aged 15–19 was 35%. A significant proportion, mainly men, informed that they had multiple sexual partners and that condom use was lower than recommended [115]. This was corroborated by a study of reproductive characteristics and utilization of preventive health services by childbearing-aged females, which revealed that the mean age at sexual initiation decreased, resulting in an increase in teenage pregnancies throughout the country [116]. This kind of national inquiry should be continued every 5 years, and the epidemiological and operational indicators of the endemic situation must be disseminated in timely fashion to direct the regional and local operational investigations for validation.

Taking into account the sexual desire present in everyone, all of this is understandable. Furthermore, cultural and religious influences bring acknowledged complexities and challenges to preventive measures practices. Moreover, the positive results of successful treatment interventions hide the dim realities of such a destructive disease and, therefore, young people are unaware of the true extent of the risks they take. Among the target population (sex workers of both genders, drug injectable users, teenagers, and the elderly) are truck drivers, as verified in a study by Teles et al. in 2005. From 620 who were interviewed, about 40% answered positively about STI antecedents (who had STI) and 70% stated that they were drug users [117].

In the study by Nardi and Rigoni, 11 harm-reduction interventions/programs in the Greater Metropolitan Porto Alegre, Rio Grande do Sul state were analyzed between 2004 and 2006 and compared with data from a previous study in 2003. They focused on the programs' sustainability and operational characteristics including different linked organizations. The results show a precarious professional situation; dependence on volunteer work to implement activities; and influence of turnover in Municipal and State administration on the continuity of projects and partnerships, as well as on the maintenance of human and financial resources. The authors conclude that "such factors lead to lack of continuity in the services provided to the target population" [118].

These different dimensions of vulnerability to sexually transmitted disease/AIDS imply health promotion actions that focus on social protection, which consider comprehensively the concept of the factors underlying vulnerability [119]. According to UNAIDS guidelines the ability of individuals and communities to avoid HIV risk may be reduced through factors beyond their control. These factors may include: lack of the knowledge and skills required to protect oneself and others; limited accessibility,

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[20]Before this prohibition in 2010, it was well known that in the case of STI, regular people used to go first to the pharmacy.

quality, and coverage of services; and restrictive societal factors, such as human rights violations, punitive laws, or harmful social and cultural norms (including practices, beliefs, and laws that stigmatize and disempower certain populations). These factors, alone or in combination, may create or exacerbate individual and collective vulnerability to HIV and other STIs [103, 117, 119, 120].

Safe-sex behavior recommendations are only successful and make a difference if there is an understanding of each context. Therefore, the practices must be based on the subjects mentioned at the beginning of this chapter: dialogue (utilizing adequate communication words) [120] in different community-based actions to enhance social status and rights of the marginalized people is only possible with the recognition of its cultural identity (knowledge and autonomy). To be able to work under this socio-constructionist principle, health and social workers should be conscious of their self-discrimination deconstruction and be trained to have an attitude of respect with values and rights of its interlocutors to function as a facilitator of the health educational process.

In conclusion, in view of these activities there are many Brazilian dermatologists dealing with these three major problems in focus at different levels of public health policies nationwide. As a tropical country there is a great demand for PHC for skin diseases, and punctual campaigns to screen HD and skin cancer at local level allow the PHC team to be trained in diagnosing and treating prevalent dermatoses. Decentralization of the health services and the use of guidelines to integrate the assistance of HD and AIDS/STI programs into the PHC system should not be to the exclusion of dermatologists. The reallocation of specialists in referral units and their participation in clinical sessions to discuss the most challenging cases contribute to best practices and permanent and multidisciplinary health education [121].

Conflict of Interest: This authors declare that there is no conflict of interest.

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Part II

Dermatologic Diseases in Public Health: Cutaneous Infectious

Hanseniasis

5

Letícia Maria Eidt

Key Point Summary
- Hanseniasis is an infectious disease, caused by *Mycobacterium leprae*, which affects principally the skin and peripheral nerves
- Reporting the disease is compulsory worldwide
- It is a public health problem because of its potential for incapacity
- Prevention of disabilities begins with the early diagnosis, followed by multidrug therapy and patient health education for self-care

Introduction

Hanseniasis (Hansen's disease) is a systemic infectious disease caused by *Mycobacterium leprae*, an intracellular and acid-fast bacterium that primarily affects the skin and peripheral nerves. If the disease progresses, other organs such as the liver, kidneys, adrenal glands, testicles, eyes, and lymph nodes can be affected. Central nervous system involvement is exceptional.

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Hanseniasis is best understood as two conjoined diseases. The first is a chronic mycobacterial infection that elicits an extraordinary range of cellular immune responses in humans. The second is a peripheral neuropathy initiated by the infection and accompanying immunologic events, but whose course and sequelae often extend many years beyond the cure of the infection and may lead to severely debilitating physical, social, and psychological consequences [1]. Both of these aspects must be considered by clinicians and health workers who deal with persons affected by the disease.

Diagnosis in the early stages of the disease creates minimal chances of progressive disability and subsequent deformities related to the evolution of bacteria in the susceptible organism. These disabilities are responsible for the stigma and prejudice against persons affected by hanseniasis.

In Brazil the recommendation is to avoid the term "leprosy" and its derivatives because of prejudice, stigma, and discrimination. As the word "leprosy" carries a very strong anti-educational burden, to honor the discoverer of *M. leprae*, Gerhard Armauer Hansen, since the year 1975 the terms "hanseniasis" and its derivatives Hansen's bacillus, hansenology, hansenologist, hansenic, hansenoma, and hanseniasis patient have been used On August 4, 1975, President Ernesto Geisel and Minister Almeida Machado introduced the word "hanseniasis" to the federal

agencies of the Ministry of Health. The historic decree marked the end of a neologism and the official beginning in Brazil of a "disease like the others" to be controlled "like the others" by the *Divisão Nacional de Dermatologia Sanitária* (Sanitary Dermatology Division). On June 1976 Minister Machado issued a bill proscribing the term "lepra" and derivatives from the documents of the Ministry of Health [2].

Later, in 1995 President Fernando Henrique Cardoso and Minister Adib Jatene issued Law No. 9.010 that prohibited the use of adjectives related to leprosy, except in informative references to history [3].

Hanseniasis is a mandatorily reported disease in the current guidelines of the World Health Organization (WHO) [4] and the Brazil Ministry of Health [5]. In Brazil, Decree number 149 of February 3, 2016, approved the Guidelines for Surveillance, Attention and Elimination of Hanseniasis as a Public Health Problem to guide managers and professionals of health services [5, 6].

Hanseniasis is a public health problem not because of the skin lesions but because of its potentially incapacitating and physical consequences, which contribute to the prejudice, stigma, and discrimination that accompany this disease.

Epidemiology

Hanseniasis remains endemic in all countries of the Southeast Asian and African regions, and in most countries of the Eastern Mediterranean region. In the Americas, locally transmitted hanseniasis is found in all countries (except Canada and Chile) and several island countries of the Caribbean. A small number of cases have been reported in several southern and eastern European countries. In the Western Pacific the disease is endemic in most countries except New Zealand and some small island nations [7].

The global registered point prevalence at the beginning of 2011 was 192,246 cases, with 228,474 new cases detected during 2010. Of these, about 95% arose from only 17 countries. These are, in order of ranking, India, Brazil,

Indonesia, Bangladesh, Democratic Republic of Congo, Ethiopia, Nepal, Nigeria, Myanmar, United Republic of Tanzania, Sudan, Sri Lanka, Philippines, China, Madagascar, Mozambique, and Angola [7]. Figures 5.1 and 5.2 show the prevalence and incidence of hanseniasis worldwide as reported to the WHO in January 2011 and January 2012, respectively.

Based on official data from Ministries of Health in endemic countries, the global annual detection of leprosy has shown a declining trend since 2001. The number of new cases detected was 407,791 in 2004, but had fallen by 2010 to 228,474 and to 219.075 in 2011, a reduction of more than 46% [8].

In Brazil, in 2014 official data reported a detection rate for new cases of 15.32 and prevalence rate of 1.27. In this year 31.064 new cases were diagnosed, 65.91% in the multibacillary forms of the disease and 6.56% with grade 2 physical disability [9]. The most endemic region is Centro-Oeste, with a prevalence rate of 3.93, while the state of Mato Grosso has the highest number of cases, with a prevalence of 10.19.

Etiologic Agent and Transmission

Hanseniasis is caused by a slow-growing bacillus, *M. leprae*, or bacillus of Hansen, discovered in 1873 by Gerhrad Armauer Hansen in Bergen, Norway [10]. In those days this disease was thought to be hereditary.

The bacillus of Hansen is an obligate, intracellular, acid-fast bacillus multiplying mainly inside the macrophages of the skin (histiocytes) and nerves (Schwann cells). It closely resembles the bacillus that causes tuberculosis. However, *M. leprae* is less acid-fast than *Mycobacterium tuberculosis* [10]. *M. leprae* can survive up to 46 days in warm, moist soil not exposed to direct sunlight and has a generation time of 12–13 days. It produces a specific substance called phenolic glycolipid 1 (PGL-1) by which it is identified [11]. Its genome has recently been sequenced, and it is hoped that this knowledge may help in developing a vaccine to combat the disease.

M. leprae is a Gram-positive bacterium that in stained skin smears or secretions is seen lying

Leprosy prevalence rates, data reported to WHO as of beginning January 2011
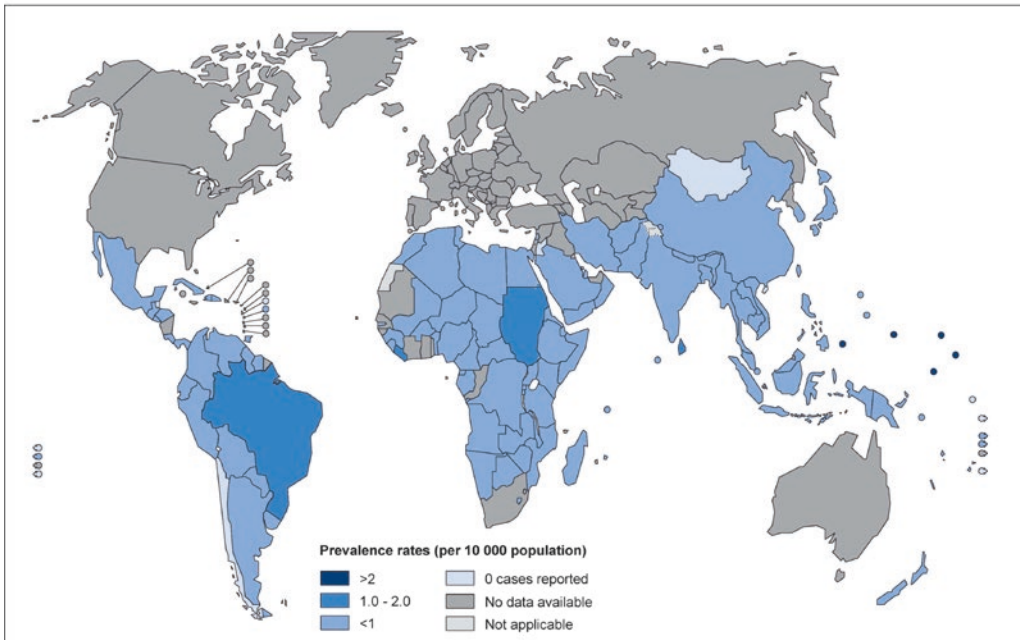
Prevalence rates (per 10 000 population)

- >2
- 1.0 - 2.0
- <1
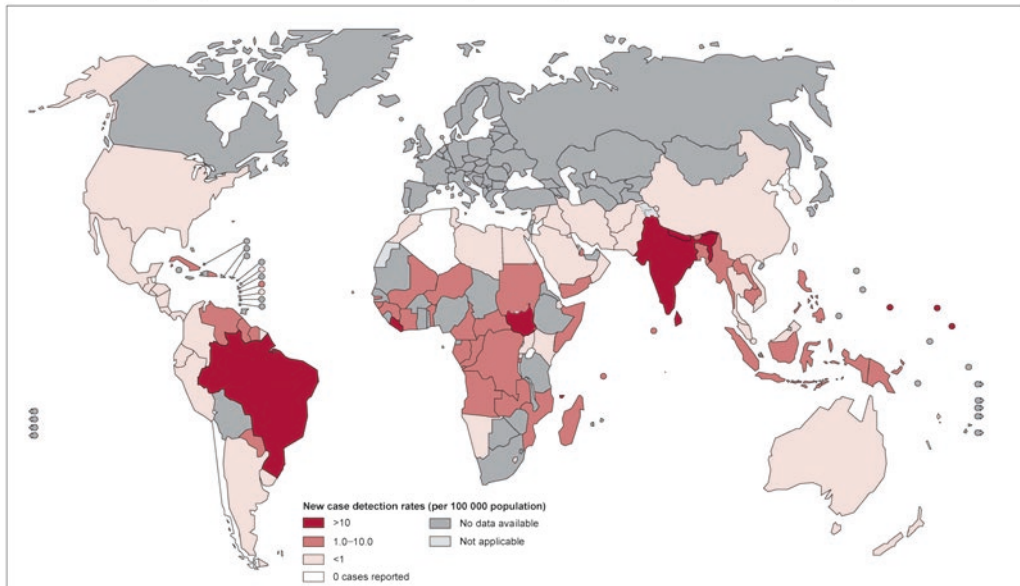- 0 cases reported
- No data available
- Not applicable

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2011. All rights reserved

Data Source: World Health Organization
Map Production: Control of Neglected
Tropical Diseases (NTD)
World Health Organization

World Health Organization

Fig. 5.1 Prevalence of hanseniasis, WHO, January 2011 (http://www.who.int/lep/situation/prevalence/en/)

Leprosy new case detection rates, data reported to WHO as of January 2012

New case detection rates (per 100 000 population)

- >10
- 1.0–10.0
- <1
- 0 cases reported
- No data available
- Not applicable

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2012. All rights reserved

Data Source: World Health Organization
Map Production: Control of Neglected
Tropical Diseases (NTD)
World Health Organization

World Health Organization

Fig. 5.2 Detection rates of new cases of hanseniasis, WHO, January 2012 (http://www.who.int/lep/situation/Leprosy_DR_2011.pdf?ua=1)

singly, in clumps, or in compact masses known as globi (Figs. 5.3 and 5.4). In smears stained by the Ziehl–Neelsen method, living and viable bacilli appear as solid and red staining. Dead and nonviable bacilli may be fragmented (showing smalls gaps in the stain) or granular, showing unstained zones across the width of the bacillus.

Bacilli of Hansen are scan in lesions of paucibacillary hanseniasis (indeterminate and tuberculoid), but are present in enormous numbers in the lesions of multibacillary hanseniasis (dimorphous and virchowian).

After the discovery of the hanseniasis bacilli, Hansen attempted repeatedly to grow them on artificial media in the laboratory, without success [1, 10]. He also made repeated, unsuccessful attempts to infect himself as well as his mentor
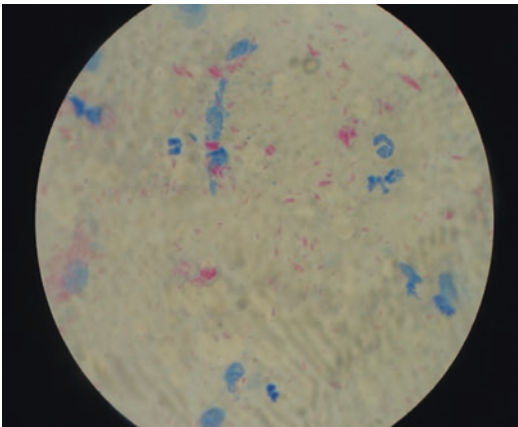
Fig. 5.3 *M. leprae* singly and in clumps
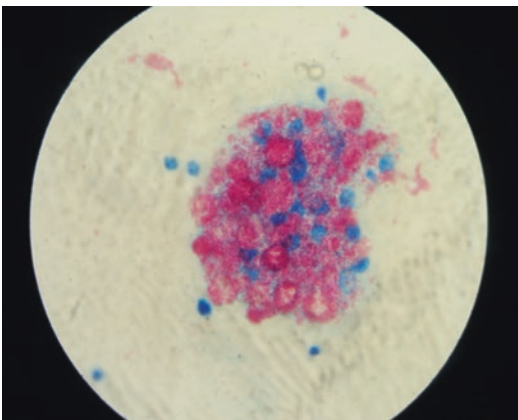
Fig. 5.4 *M. leprae* in globi

and father-in-law, Dr. Danielssen, with material from his patients. Danielssen had four inoculations, all of which ended in negative results, because hanseniasis is not easily communicable and not highly infectious [4, 10].

The precise mechanism of transmission of *M. leprae* is unknown [1]. The contact does not need to be skin to skin as was previously believed because the nose, and not the skin, is the main port of exit of bacilli from multibacillary patients [10]. Therefore the most accepted mechanism of transmission is via the upper airways with bacilli being eliminated by droplets from the nose and mouth of untreated patients with severe disease [4]. Untreated hanseniasis patients may discharge as many as 100 million (10^8) bacilli of Hansen from their nasal secretions every day, whereas these bacilli are rarely found on the intact skin of patients with multibacillary hanseniasis [10].

The inhalation of bacilli-laden droplets is currently regarded as the most likely mode of entry of *M. leprae* into contact persons. Inhaled bacilli of Hansen probably enter the body through the nasal mucosa. A scratched or abraded skin may facilitate the passage of organisms in droplets deposited on the skin surface, through the epidermis, and into the dermis. The nasal mucosa and abraded or damaged skin are the two preferred sites of entry of bacillus of Hansen. These sites have a temperature lower than the normal body temperature of 37 °C [10].

The infected human being is considered to be the only source of infection. The infective capacity of multibacillary cases is 4- to 11-times greater than paucibacillary hanseniasis [10]. Untreated patients with multibacillary hanseniasis thus constitute the main source of infection. The occurrence or non-occurrence of the disease is closely associated with the cell-mediated immune response of the host to the challenge by the bacillus of Hansen [10, 11].

In general, prolonged or close contact is considered to be necessary for transmission. However, in susceptible persons even a casual or short contact may cause the disease. An intrafamilial contact with a multibacillary patient is more risky than an occasional extrafamilial one [10]. It is assumed that 95% of the population is resistant to

infection with *M. leprae.* People of all ages are susceptible to the disease, but the age of onset is determined by the opportunities available for the person to come into contact with bacilli [11].

Although bacilli of Hansen have been detected in sperm, ovary, umbilical cord, placenta, and even the fetus, the possibility of congenital transmission of hanseniasis is remote [10].

Clinical Presentation and Classification

The clinical manifestations of hanseniasis are varied and are determined by the host–parasite relationship, which varies according to the degree of resistance possessed by the host [11]. Owing to the fact that *M. leprae* is an obligate intracellular microorganism, the resistance to illness depends on the cellular immunity of the host.

Most individuals who have been in contact with persons affected by multibacillary hanseniasis develop a subclinical infection. However, in more than 95% of such persons, the infection fails to establish itself and they never develop any manifestation of the disease [10]. In turn, less than 5% of people exposed to *M. leprae* develop clinical disease [12] and only a single or a few ill-defined hypopigmented or faintly erythematous patches of indeterminate hanseniasis may develop.

The incubation period of the disease may vary from 3 months [12] to 30 [11] or 40 [12] years, with an average of 3–5 years [11], although 5–7 years is typical [12]. For paucibacillary disease the incubation period is up to 5 years, and 20 years or longer for multibacillary hanseniasis [12].

The disease is classified by taking into account the clinical aspects, bacteriologic status, immunologic behavior, and histologic characteristics in a given individual [11]. Hanseniasis clinically manifests in a variety of clinical forms related to the type and strength of the host's immune response. A strong cellular immune response, present in those subjects with fairly high resistance, is effective in curtailing *M. leprae* multiplication and leads to a localized form of the disease. However,

in those with low resistance against *M. leprae* a severe generalized form of the disease is produced. Between the two polar forms there exists a wide spectrum of manifestations [11, 13].

Of several classifications that have been formulated over the years, two are widely accepted: the Ridley–Jopling classification and the operational classification proposed by the WHO.

The WHO classification [5, 10, 12, 13] is very simple and divides hanseniasis patients into two groups according with the number of skin lesions: paucibacillary (PB) and multibacillary (MB) (see Box 5.1).

- **Paucibacillary** (**PB**): one to five skin lesions;
- **Multibacillary** (**MB**): six or more skin lesions.

The WHO classification system is used in the field for choosing an appropriate treatment regimen. This is particularly useful when reliable facilities for skin smear examination are not available.

> **Box 5.1 Important note**
> If bacteriologic examination of skin smear shows a positive result then the patients are grouped into MB leprosy, irrespective of lesser number of skin lesions.
>
> In doubt, patients should be classified as Multibacillary.

The Ridley–Jopling classification is based on the immunity of the patient, which is reflected in the clinical, histopathologic, and bacteriologic changes. Under this classification there are two polar groups, tuberculoid and virchowian, and a spectrum of manifestation with three immunologically unstable groups: dimorphous tuberculoid, dimorphous dimorphous, and dimorphous virchowian. The earliest manifestation of the disease is termed indeterminate, characterized by a minimal clinical response to the infection, no clearly defined immune status, and sparse bacteriologic and histopathologic findings. For these reasons it offers the greatest difficulty in arriving at a diagnosis [10–12].

Indeterminate Hanseniasis

Indeterminate hanseniasis (IH) clinically manifests as one or a few hypopigmented macules with vague margins and a few centimeters in diameter. In fair skin hypopigmentation may not be clearly evident, but there may be erythema (Figs. 5.5 and 5.6). There may be sensory loss of temperature discrimination or ability to feel light touch [11, 12]. The lesions appear to be dry and

Fig. 5.5 Indeterminate hanseniasis on the extensor surface of the arm

Fig. 5.6 Indeterminate hanseniasis on the lateral surface of the leg

are usually present on the extensor surface of the extremities, buttocks, or face, which are colder body areas, although they can occur anywhere in the body [11]. The peripheral nerves trunks are normal [10].

Indeterminate hanseniasis should be self-limited or may progress to other forms of the disease [10]. However, the importance of identifying the disease at this early stage cannot be overemphasized [11]. Sometimes it is difficult to diagnose indeterminate hanseniasis with certainty and in such circumstances the patients should be examined at 3- to 6-monthly intervals to assess the progress of the lesions [10].

Skin smears are almost always negative. Histologic examination of the skin shows no significant change in the epidermis, and there is minimal inflammation in the dermis with focal collections of lymphocytes and histiocytes aggregated around blood, dermal nerves, sweat glands, and other skin annexes [11].

Tuberculoid Hanseniasis

This form occurs in individuals with high, but not complete resistance against *M. leprae*. Symptoms may be cutaneous, neural, or both. The skin lesion of tuberculoid hanseniasis is usually single, but there may be two or three asymmetrically distributed well-demarcated plaques or flat-patch lesions, seldom over 10 cm in diameter [10–12]. These characteristics of well-defined lesions, limited diameter, and sparseness occur because of the cell-immunologic response against *M. leprae*, which is an obligate intracellular bacillus.

Tuberculoid lesions may be hypopigmented, reddish or brownish lesions with well-defined margins. They are usually oval or rounded in shape and are well demarcated from the normal surrounding skin by a distinct edge [10]. The lesions are dry and tend to be hairless [11, 12]. The lesions occur on cooler areas of the body rather than warmer areas such as the scalp, axillae, groin, or perineum [12].

Sensation is markedly impaired or lost in tuberculoid lesions. Well-defined edges and sensory loss of feeling for temperature, pain, or

Fig. 5.7 Tuberculoid hanseniasis: demarcated plaques
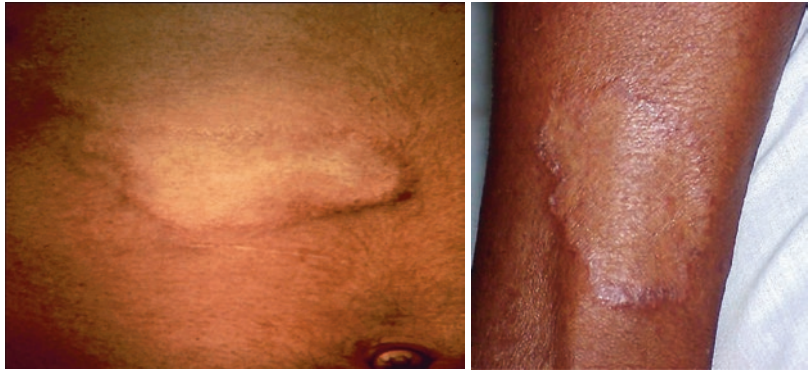
touch are characteristic features of tuberculoid hanseniasis [10]. Temperature discrimination may be the first sensory modality lost [12]. About 30% of nerves have to be destroyed before sensory impairment can be detected; therefore, pain may be the first neurologic symptom. Often an enlarged nerve is palpable near the skin lesion. For example, if there is a skin lesion near the elbow the ulnar nerve may be enlarged [12].

Skin smears are negative for acid-fast bacilli. Histologic examination of the skin shows atrophy of the epidermis and some areas of minimal hyperplasia. There are discrete and confluent tuberculoid granulomas in the dermis, sometimes with Langhans giant cells present [11, 12] (Fig. 5.7).

Virchowian Hanseniasis

Virchowian hanseniasis occurs in those persons who possess virtually no resistance to infection by *M. leprae*. The bacilli multiply and spread to affect almost the entire skin, all the dermal and subcutaneously placed peripheral nerves, as well as the mucous membrane of the upper respiratory tract, anterior aspect of the eyes, lymph nodes, liver, spleen, bone marrow, testes, and adrenal glands [11]. It is usually a generalized disease [10].

The skin lesions are disseminated and are classified as macular, finely infiltrated, grossly infiltrated, and nodular [11]. Diffuse dermal infiltration is always present and can be nodular or non-nodular. Findings can include small hypopigmented macules, symmetrically distributed all over the body, or virchowian infiltrates that can be diffuse, plaque-like, or nodular. Macules are ill defined and show no sensory loss [10, 12], with poorly defined margins [10, 12]. Sweating is eventually lost. Hair loss starts over the lateral third of the eyebrow [10, 12] and then may involve the eyelashes (madarosis) and the body, but scalp hair is preserved [12].

Infiltrated virchowian hanseniasis is the stage that succeeds the macular form. The infiltrate plaques are glossy, soft, and slope toward the periphery. Sensory loss is slight or negligible in the infiltrated areas [10].

Nodular lesions, or hansenomas, are present in still more advanced forms of virchowian hanseniasis. These lesions are due to marked aggregation of the infiltrate and may be of the normal skin color, erythematous, or copper-colored. They may be small or large, soft or hard, and sessile or pedunculated [10]. Nodular infiltration can be seen on acral parts: earlobes, nose, chin, elbows, hands, buttocks, and knees. These nodules can enlarge and destroy underlying structures such as nasal cartilage, causing a saddle-nose deformity, and erode the alveolar ridge, leading to loss of teeth. Epistaxis is a common early finding. Leonine facial nodular infiltration can be seen in advanced disease [12].

Sensory loss tends to be symmetric over the distal limbs, starting in a glove-and-stocking distribution.

It is important to emphasize that as virchowian hanseniasis is a systemic disease, the involvement of other organs usually occurs. Bone

involvement can contribute to osteoporosis and fractures. Testicular involvement can result in gynecomastia and testicular atrophy with complaints of impotence and infertility [12]. Other complications include neuritis, laryngitis, arthritis, and iridocyclitis [11].

Skin smears are always positive (5+ to 6+) for acid-fast bacilli. Skin histology shows flattening of the epidermis with a clear Grenz zone, with a deeper diffuse foamy histiocytic infiltrate with few lymphocytes and plasma cells. The foamy appearance is a result of lipids in the *M. leprae* walls, and a Ziehl–Neelsen stain shows numerous acid-fast bacilli in globi or lying freely within the dermis [12] (Fig. 5.8).

There are two special forms of virchowian hanseniasis: Lucio hanseniasis and histoid hanseniasis. *Lucio hanseniasis* is characterized by a diffuse widespread infiltration of the skin with no formation of nodules, loss of body hair, loss of eyebrows and eyelashes, and widespread sensory loss. The skin contains numerous bacilli. This form is due to the total lack of host resistance and is rare outside Mexico and Central America. In older patients diffuse dermal infiltration may smooth out the wrinkles on the face, resulting in a youthful appearance, sometimes called "pretty leprosy" [10]. *Histoid hanseniasis* is characterized by the formation of firm, erythematous or copper-colored, glistening nodules and/or plaques in the skin of multibacillary patients who have discontinued their treatment or because bacilli have become drug resistant [10].

Dimorphous Hanseniasis

Dimorphous hanseniasis is the most commonly encountered type of the disease [10]. In this form the host immunity floats/varies, and manifestations of tuberculoid and virchowian hanseniasis can be found in the same patients. According to the extent of immunity, this group may be subdivided into dimorphous-tuberculoid, dimorphous-dimorphous, and dimorphous-virchowian.

Dimorphous hanseniasis lesions may be erythematous or copper-colored infiltrated patches, raised in the center (dome-shaped) and sloping toward the periphery, presenting an inverted saucer appearance (Fig. 5.9). Skin lesions of dimorphous hanseniasis usually have asymmetric distribution. Depending on the patients' position in the immunologic spectrum, the macular and other lesions vary greatly in number, size, and shape. The nearer the patient is to the virchowian end of the spectrum, the more numerous, shinier, less well defined, and less anesthetic they are. The nearer the patient is to the tuberculoid spectrum, the fewer are the lesions found and the more defined is the lesion margin [10].

Fig. 5.8 Virchowian hanseniasis: nodular lesions

Fig. 5.9 Dimorphous hanseniasis: infiltrated patches

The damage to nerves is widespread and frequently leads to crippling deformities. It is in this type of Hanseniasis that the most extensive and serious effects of nerve damage are seen [10].

Diagnosis

The diagnosis of hanseniasis is clinical, based on a good anamnesia and physical examination of the skin and nerve trunks. Some laboratory tests help and complement the clinical examination, but they do cannot make the diagnosis alone (see Box 5.2).

Laboratory tests (histopathology, slit skin smear, and serology), when available, may be used to help in the correct classification of these patients, especially in referral centers. However, they are not available in most health centers [14].

Approximately 70% of hanseniasis patients can be diagnosed by the single sign of skin patches with sensory loss, and the recognition of this sign should be taught as widely as possible. However, 30% of patients, including many multibacillary patients, do not present with this sign. Enlargement of one or more nerves is an important additional sign, to be supplemented by skin smears, if available and of assured quality [15].

Box 5.2 Important note
The accurate diagnosis of hanseniasis is of fundamental importance to all aspects of its epidemiology, case management, and prevention of disability. Underdiagnosis will allow continued transmission of the disease and much needless individual suffering, whereas overdiagnosis will involve overtreatment with antibiotics and unnecessary stress and stigma for some people [16].

Clinical Examination

After taking the patient's case history with regard to complaints, past treatment, places of residence, contact with other hanseniasis patients, and so forth, the entire body should be examined under adequate lighting. The examiner should look for hypopigmented areas, erythematous or copper-colored macules, infiltration, and nodules. Sensory loss is present in the majority of hanseniasis patients and often occurs in the following order: temperature → pain → touch [10].

The sensitivity screening test should be done by testing the suspected area compared with normal

skin area after correct explanation thereof to the patient (see Box 5.3). After the patient is made familiar with the test procedure it should be carried out with the patient's eyes fully closed. The diagnosis of paucibacillary forms and especially of tuberculoid hanseniasis depends on this simple procedure [10].

Box 5.3 Important note

The presence of one or more chronic skin lesions associated with anesthesia or hypoesthesia should suggest hanseniasis.

Nerve Examination

The nerves usually affected by *M. leprae* should be palpated for size, consistency, and tenderness. The nerve trunks to be examined are great auricular, supraorbital, radial, ulnar, median, lateral popliteal, and posterior tibial (Fig. 5.10). The affected nerve may be thickened and may show abscess formation. In a reactional state, the nerve will be spontaneously painful or tender to palpation.

Fig. 5.10 Enlargement of the great auricular nerve

General Examination Looking for Complications

As part of a general examination, it is important to be alert for evidence of complications of hanseniasis at the moment of diagnosis [17]. If the complications are present they should be treated with multidrug therapy (MDT).

While examining the head special attention should be paid to the eyes and the mucous of the nose and oropharynx. As part of the eye examination the clinician must look for madarosis or loss of eyebrows and eyelashes, lagophthalmos, inverted lashes of entropion, redness of conjunctivitis, and haziness of opacity of the cornea. At the nose one should look for collapsed nose, crusting, and epistaxis, and in the mouth for infiltration, nodules, or ulceration, especially on the palate.

During examination of the trunk one should check for gynecomastia, which arises secondary to orchitis and atrophy of the testes.

Complications of hanseniasis are common in the extremities as a result of nerve damage. There may be paralysis and atrophy of intrinsic muscles of the hands and feet with clawing. Because of the anesthesia, injury to hands and feet goes unrecognized by the patient, and trauma from any cause can result in ulceration.

Complementary Examinations

See Box 5.4.

Bacilloscopy

Bacilloscopy or skin smears should be taken from all patients suspected of having hanseniasis, but only in the multibacillary group (virchowian and dimorphous hanseniasis) will it be positive. Therefore, a negative result does not exclude a diagnosis of hanseniasis.

Before taking the smear, the lesion must be cleaned with alcohol or ether. The smear should be taken from the most active-looking part of the lesion. The site of the smear should be gripped between the thumb and forefinger to press out the blood. With a sterile small-bladed scalpel an inci-

sion 2–3 mm deep is made in the skin of the patient. The blade is then turned until it is at right angles to the incision and the wound is scraped firmly two or three times in the same direction so that a drop of dermal tissue collects on its tip. This drop of tissue fluid and pulp is gently smeared over a circular area on a glass slide. Skin smears should not contain blood because blood can interfere with the Ziehl–Neelsen method of staining [10].

After staining the smears are read. For this purpose the Bacteriologic Index is used, which indicates the density of Hansen's bacilli in smears and includes both solid-staining and fragmented or granular bacilli. According to Ridley's logarithmic scale, this ranges from zero (no bacilli) to 6+ (more than 1,000 bacilli on average and presence of globi). This scale is based on the number of bacilli seen in an average microscopic field of smear using an oil-immersion objective [10].

Slit skin smear is the test usually performed to confirm the operational diagnosis of leprosy. This helps to distinguish between paucibacillary and multibacillary hanseniasis. However, the test requires trained personnel for sample collection and reading, and is relatively invasive [14].

Skin Biopsy

Skin biopsy for histopathologic evaluation should be used as complementary examination for diagnosis and classification of hanseniasis. The characteristic histologic findings are as follows [10, 11].

Indeterminate hanseniasis: A diagnostic problem both for the clinician and the pathologist because the clinical picture is vague and the pathologic changes are nonspecific. The epidermis is normal. In the dermis there are small clusters of mononuclear cells (mainly lymphocytes and a few histiocytes) around blood vessels, nerves, and dermal appendages, with selective involvement of the neurovascular bundles. Usually there is no granuloma (Fig. 5.11).
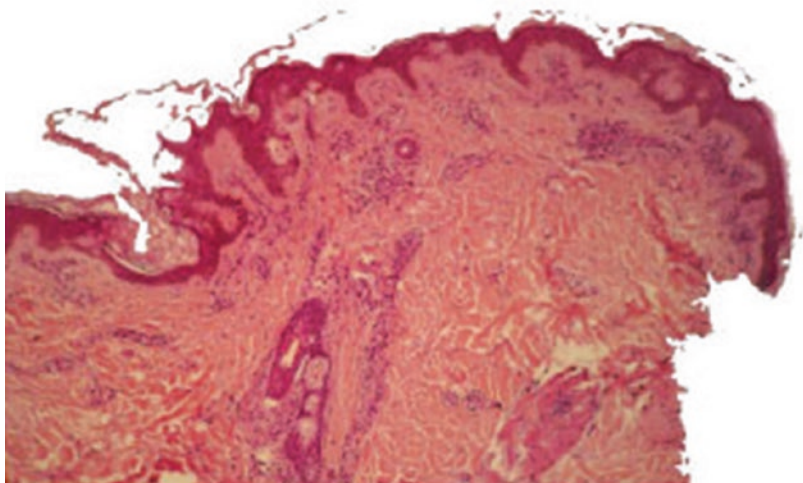
Fig. 5.11 Histopathology of indeterminate hanseniasis: perineural and perivascular lymphocytic infiltrate

Tuberculoid hanseniasis: Typical tubercles comprising epithelioid cells, Langhans giant cells, and surrounding zone of lymphocytes are found in the dermis. The granuloma may extend into and erode the basal layer of the epidermis. Cutaneous nerves are infiltrated and often destroyed (Fig. 5.12).

Virchowian hanseniasis: The epidermis shows thinning and flattening of rete ridges. The characteristic histologic finding is a diffuse, highly baciliferous granuloma in the dermis. The granuloma mainly consists of macrophage cells that fail to differentiate into epithelioid cells. Instead they become mere sacs containing multiplying Hansen's bacilli. Lymphocytes are absent or scant and there is no attempt to surround macrophages. In the late stages, the cytoplasm of macrophages undergoes fatty changes, resulting in the formation of Virchow's foamy cells (Fig. 5.13).

Fig. 5.12 Histopathology of tuberculoid hanseniasis: tuberculoid granuloma
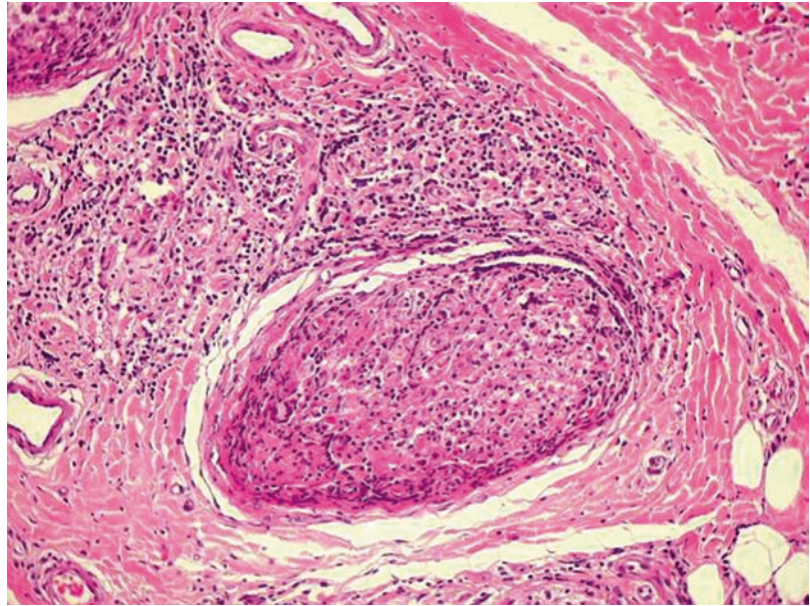
Fig. 5.13 Histopathology of virchowian hanseniasis
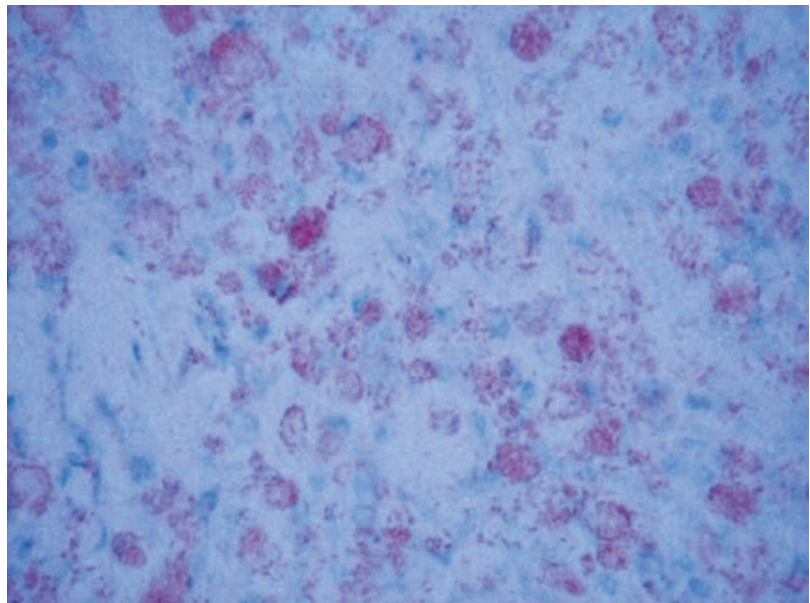
Fig. 5.14 Histopathology of dimorphous hanseniasis: lymphohystiocytic, superficial, and deep infiltration with giant cells (H&E). Negative BAAR (Z-N)
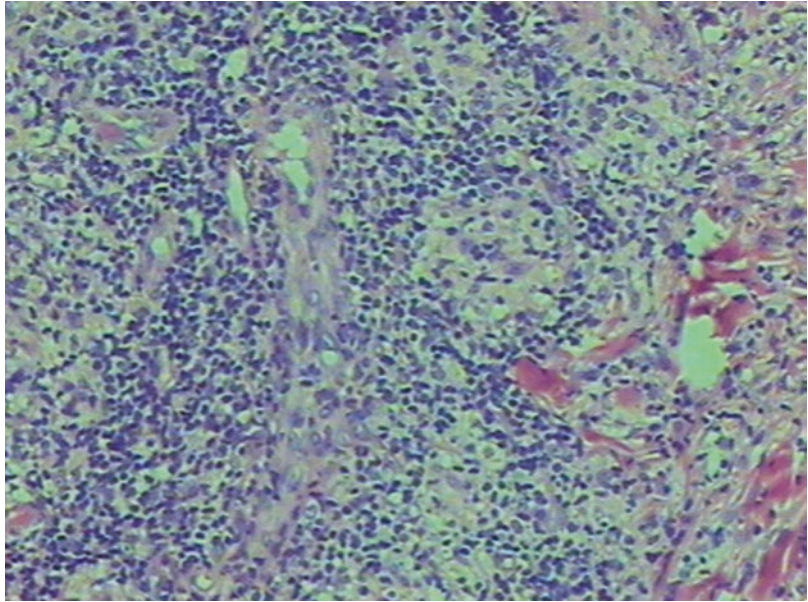
Dimorphous hanseniasis: As this group is inherently unstable in accordance with the immunologic response of the host against the *M. leprae*, the findings at the histologic examination are also unstable. Sometimes tuberculoid hanseniasis is brought to mind while on other occasions characteristics of virchowian hanseniasis are observed (Fig. 5.14).

ML Flow

In 2003 a method called ML Flow, an alternative to ELISA (serology) for detection of anti-PGL-1 immunoglobulin M antibodies (IgM), was described by Bührer Sékula et al. Rather than a method for diagnosis, this is an examination to classify patients as paucibacillary or multibacillary and to help decide on their therapy. It does not appear to cross-react with other mycobacterioses [14].

Pilocarpine

Testing with pilocarpine nitrate may help in the diagnosis of non-virchowian cases of hanseniasis, especially for patients in whom sensory impairment cannot be definitively determined. The use of this substance causes sweating in intact skin; in skin affected by leprosy, sweat production does not occur [10].

According to the WHO, hanseniasis should be suspected in individuals with any of the following symptoms or signs [13]:

- Pale or reddish patches on the skin
- Loss or decrease of feeling in the skin patch
- Numbness or tingling of the hands and feet
- Weakness of the hands, feet or eyelids
- Painful or tender nerves
- Swelling or lumps in the face or ear lobes
- Painless wounds or burns in the hands or feet

According to the International Leprosy Association, three cardinal signs remain the basis for the clinical diagnosis of hanseniasis [16]:

- Anesthetic skin lesions
- Enlarged peripheral nerves
- Acid-fast bacilli in the skin smear

Any one of these signs has been regarded as sufficient for the diagnosis of hanseniasis, so that sensitivity is high.

Uncomplicatedly, WHO recommends that hanseniasis diagnosis is confirmed when at least one of the following cardinal signs is present [13]:

- Definite loss of sensation in a pale or reddish skin patch
- A thickened peripheral nerve with loss of sensation and/or weakness of the muscles supplied by that nerve
- Presence of acid-fast bacilli in a slit skin smear

Differential Diagnosis

According to different authors hanseniasis may be confused with other dermatoses [10–12]. Cutaneous lesions of hanseniasis clinically mimic many common and some uncommon skin diseases. A careful clinical examination, especially to detect impairment of sensation over the lesions, is important for the diagnosis of hanseniasis lesions.

Dermatologic diseases that clinically resemble Hanseniasis are listed below.

Indeterminate hanseniasis: *Pityriasis alba*, *Pityriasis versicolor*, postinflammatory hypopigmentation, hypopigmented (early) vitiligo, seborrheic dermatitis, nutritional hypopigmentation, occupational leukoderma, and birth marks (*Naevus anaemicus* or *achromicus*)

Tubeculoid hanseniasis: *Lupus vulgaris*, *Tinea circinata*, tertiary syphilis, sarcoidosis, tuberculoid, granuloma annulare, necrobiosis lipoidica, erythema annulare centrifugum, granuloma multiforme, psoriasis vulgaris, discoid lupus erythematosus, and ptyriasis rosea

Virchowian hanseniasis: neurofibromatosis, multiple lipomatosis, keloids, lymphoma, mycosis fungoides, molluscum contagiosum, and leishmaniasis

Dimorphous hanseniasis: mycosis fungoides, pharmacodermias, and lymphoma

Treatment

Treatment for patients affected by hanseniasis consists of drugs (antibiotics), moisturizers, sunscreen, guidance for self-care, emotional support, and health education (see Box 5.5) [18–20].

Box 5.5 Important note
When a patient has completed his course of treatment, 6 blisters for the paucibacillary group and 12 blisters for the multibacillary group, he is considered to be cured and treatment is therefore stopped, regardless of the presence of residual lesions or disabilities and deformities.

The first successful drug used for the treatment of hanseniasis was dapsone at a leprosarium in Carville, Louisiana, USA in 1943, and for many years it was used as a monotherapy. It inhibits acid folic synthesis by competitive inhibition and is bacteriostatic. Clofazimine was first used for hanseniasis treatment in 1962 and its mechanism of action, though still not elucidated, is also bactericidal and anti-inflammatory. Rifampicin is currently a key bactericidal antibiotic and has been used since the 1970s [21, 22].

Prior to the advent of MDT these three drugs (dapsone, rifampicin, and clofazimine) were administered alone, although rifampicin had been used in combination with dapsone. Gradually, clinical and experimental evidence of resistance to dapsone and rifampicin came to light [23–26]. Dapsone is still a fundamental agent against *M. leprae* even in the MDT era, despite reports of resistance in 1953, less than 10 years from the beginning of its use. Although clofazimine has been used for over five decades, reported drug resistance is rare [22, 27]. Issues relating to drug resistance are so important that sentinel surveillance for drug resistance in hanseniasis by the Global Leprosy Program was launched in 2006 [28].

The situation surrounding drug resistance prompted the WHO to recommend therapeutic regimens involving two or three of these drugs. This MDT, as it is known today, was first proposed by the WHO in 1982 [10, 22, 29] and involves a combination of drugs that are safe and effective in treating hanseniasis and preventing the emergence of drug resistance [21, 27, 30].
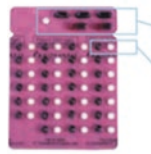
MDT Regimens

Each blister pack contains treatment for 4 weeks.

It is crucial that patients understand which drugs they have to take once a month and which every day.

PB adult treatment:
Once a month: Day 1
– 2 capsules of rifampicin (300 mg x 2)
– 1 tablet of dapsone (100 mg)
Once a day: Days 2–28
– 1 tablet of dapsone (100 mg)
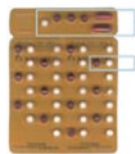**Full course:** 6 blister packs

PB adult blister pack

PB child treatment (10–14 years):
Once a month: Day 1
– 2 capsules of rifampicin
  (300 mg+150 mg)
– 1 tablet of dapsone (50 mg)
Once a day: Day 2–28
– 1 tablet of dapsone (50 mg)

Full course: 6 blister packs

PB child blister pack

For children younger than 10, the dose must be adjusted according to body weight.

MB adult treatment:
Once a month: Day 1
– 2 capsules of rifampicin (300 mg x 2)
– 3 capsules of clofazimine (100 mg x 3)
– 1 tablet of dapsone (100 mg)
Once a day: Day 2–28
– 1 capsule of clofazimine (50 mg)
– 1 tablet of dapsone (100 mg)
Full course: 12 blister packs

MB adult blister pack

MB child treatment (10–14 years):
Once a month: Day 1
– 2 capsules of rifampicin (300 mg+150 mg)
– 3 capsules of clofazimine (50 mg x 3)
– 1 tablet of dapsone (50 mg)
Once a day: Day 2–28
– 1 capsule of clofazimine every other day
  (50 mg)
– 1 tablet of dapsone (50 mg)

Full course: 12 blister packs

MB child blister pack

For children younger than 10, the dose must be adjusted according to body weight.

Fig. 5.15 Blisters of standard multidrug therapy (MDT). Regimen treatments for adults (*green* and *pink* blisters) and children ages 10–14 (*blue* and *orange* blisters) (Source: http://www.searo.who.int/entity/global_leprosy_programme/en/)

Under no circumstances should hanseniasis be treated by a single drug [31, 32].

MDT is provided in convenient packs covering a month of treatment, is available free of charge to all who need it, and the drugs are all taken by mouth. There are different packs with the same drugs, but in smaller doses, for children.

The standard MDT (rifampicin, dapsone, clofazimine) can be used in special cases such as women and their babies during pregnancy and breast-feeding, children, HIV-positive patients on anti-retroviral treatment, and patients being treated for tuberculosis. If a patient with hanseniasis is treated for tuberculosis, the MDT regimen should omit rifampicin as long as the tuberculosis regimen contains rifampicin.

MDT treatment is provided in specific blister packs and is available for multibacillary and paucibacillary hanseniasis as well for adults and children (Fig. 5.15) [10, 31, 32]. The standard treatment regimen for multibacillary and paucibacillary hanseniasis is shown in Table 5.1:

For children under 10 years of age the appropriate dose can be decided on the basis of body

Table 5.1 Standard multidrug therapy (MDT) regimen treatment for adults and children (ages 10–14)

MDT-PB treatment regimen for adult	
Rifampicin	600 mg once a month
Dapsone	100 mg once a month and 100 mg daily
	Duration: 6 blister packs
MDT-MB treatment regimen for adult	
Rifampicin	600 mg once a month
Dapsone	100 mg once a month and 100 mg daily
Clofazimine	300 mg once a month and 50 mg daily
	Duration: 12 blister packs
MDT-PB treatment regimen for child	(age 10–14)
Rifampicin	450 mg once a month
Dapsone	50 mg once a month and 50 mg daily
	Duration: 6 blister packs
MDT-MB treatment regimen for child	(age 10–14)
Rifampicin	450 mg once a month
Dapsone	50 mg once a month and 50 mg daily
Clofazimine	150 mg once a month and 50 mg every other day
	Duration: 12 blister packs

Adapted from WHO, 2009 [32]

weight. The standard child blister pack may be broken up so that the appropriate dose is given to children younger than 10 years (Table 5.2).

Sometimes it will be necessary to treat a patient with a high bacillary index with additional 12-blister packs. However, this decision may only be taken by specialists at referral units after consideration of the clinical and bacteriologic evidence [31, 32].

Despite standard MDT being safe and serious adverse effects being rare, they may occur. The most common adverse effects are listed in Table 5.3.

If one or more of the standard drugs must be stopped, other drugs are available such as ofloxacin [33], minocilin, and clarithromycin, but these must be managed by a specialist. In the case of ofloxacin, some drug resistance has been reported [34–36]. All of these drugs have bactericidal activity (see Box 5.6).

Hanseniasis is curable with MDT recommended by the WHO since 1982. However, it is fundamental to lend emotional support to the patients, who should be treated with respect,

> **Box 5.6 Important note**
> Rifampicin is an exceptionally potent bactericidal agent against *M. leprae*. A single dose of 600 mg is capable of killing more than 99.9% of viable organisms.
>
> Because of the risk of drug resistance, under no circumstances should hanseniasis be treated by a single drug.

patience, and understanding. Besides medical treatment, they need support and reassurance from family, friends, and health workers to help them achieve self-esteem and self-respect and to lead a normal life [10, 18, 19].

MDT treatment works slowly and may not, on its own, cure anesthesia, claw hand, or ulcers. In patients who do not understand the limitations of the antibiotics they may be discouraged, stop treatment too soon, and relapse. Health education is therefore an essential part of the hanseniasis treatment. The things the patient must know are known as the "six D's of health education" [20]:

1. **D**uration: how long he will need to take his treatment
2. **D**rugs: tablets and capsules are used for curing Hanseniasis
3. **D**isappearing skin patches: the skin patches never disappear quickly

Table 5.2 Doses of MDT drugs for children under 10 years age

Rifampicin	10 mg per kilogram body weight
Dapsone	2 mg per kilogram body weight daily and monthly
Clofazimine	1 mg per kilogram body weight daily
	6 mg per kilogram body weight monthly

Adapted from WHO, 2009 [32]

Table 5.3 Adverse effects of standard MDT drugs

Drug	Adverse effects	Management
Rifampicin (RFM)	Red urine	Orientation/counseling
	Jaundice	Stop RFM
	Flu-like syndrome (shock, purpura, renal failure)	Stop RFM
	Gastro-intestinal upset	Give DDS with food
Dapsone (DDS)	Anemia	Give iron and folic acid
	Jaundice	Stop DDS
	Rash, urticaria, allergy	Stop DDS
	Gastro-intestinal upset	Give DDS with food
Clofazimine (CFZ)	Xerosis	Moisturizer/counseling
	Hyperpigmentation and brown discoloration of skin	Sunscreen/counseling

Adapted from WHO, 2009 [32]

4. **D**isability: deformity and impaired sensation which are present at the start of treatment often improve but may not recover completely even when the disease is fully cured
5. **D**iet: no diet restrictions are necessary to use dapsone, clofazimine, and rifampicin
6. **D**angers: patients should be warmed of the symptoms or reaction and advised to come for an extra anti-reaction treatment if necessary

Reactions and Its Management

During the usually chronic course of hanseniasis, acute inflammatory episodes (called reactions) may occur. These immunologic reactions are an important aspect of hanseniasis that significantly affects the course of the disease and the associated disability. It is important to remember that the impairment of nerve function occurs throughout the infectious disease course but also occurs through immunologic reactions that often rapidly accelerate the nerve damage [37].

Any type of hanseniasis, except an early indeterminate form, may undergo a sudden inflammatory phase of exacerbation. Reactions are more common in patients with multibacillary hanseniasis (virchowian and dimorphous categories) [10].

Reactions may occur spontaneously or may be precipitated by intercurrent infections, anemia, mental or physical stress, inflammatory processes, puberty, pregnancy, parturition, vaccinations, or surgical interventions. Some drugs such as vitamin A, progesterone, bromides, and iodides also may precipitate reactions [10, 12], although in some cases precipitating factors may not be obvious [10]. The reactions may occur before, during, or after treatment with MDT [37].

There are two main types of reaction that affect 30%–50% of patients: type 1 reaction (reversal reaction) and type 2 reaction (erythema nodosum hansenic) [10, 37]. To Worobec [12], at least 50% and possibly a much higher percentage of dimorphous patients will experience reactional states after initiating MDT. According to Kamath et al. [37], the third reaction (Lucio phenomenon) is relatively rare, occurring only in a diffuse non-nodular virchowian hanseniasis (lepra bonita). However, the manifestations can be dramatic, with patients developing widespread skin necrosis.

These reactions are often incorrectly viewed as complications or adverse effects of MDT and are also confused, sometimes, with relapses.

Regardless of the type of reactions or when they occur, any reaction is a medical emergency, greatly increasing hanseniasis-related morbidity. It is important to specifically recognize and treat reactions to reduce the burden of disability in hanseniasis [37].

Type 1 or Reversal Reaction

Reversal reactions most commonly occur in dimorphous forms of hanseniasis (dimorphous tuberculoid, dimorphous dimorphous, and dimorphous virchowian) [37], an may also occur in tuberculoid hanseniasis [10]. This reaction is an example of the type IV hypersensitivity (allergic) reaction of Coombs and Gell [10] and is the result of increasing (upgrading) cell-mediated immune response or decreasing (downgrading) cell-mediated immune response to *M. leprae* [12].

Clinically, patients display abrupt inflammatory changes of the skin, nerves, or both. Existing skin lesions become erythematous and edematous and resemble erysipelas. In severe cases necrosis and ulcerations may occur [10]. Associated signs include erythema and edema of hands, feet, and face (Fig. 5.16), silent neuritis, pain or tenderness of nerves, and new erythematous and edematous papules, plaques, and nodules [12]. Accompanying edema of the hands and feet is common, whereas systemic symptoms are unusual.

Fig. 5.16 Type 1 reaction

Reversal reaction is the leading cause of nerve damage in hanseniasis and may lead to permanent disability. Spontaneous nerve pain, weakness, or paresthesia signals neuritis, whereas nerve function impairment is defined as clinically detectable reduced motor and sensory function. The ulnar, median, radial, common peroneal, posterior tibial, and facial nerves are most commonly involved, leading to wrist drop, foot drop, and facial palsy. Sometimes patients can lose protective pain sensation, increasing their vulnerability to injury [37].

Type 2 or Erythema Nodosum Hansenic (ENH)

This reaction involves humoral hypersensitivity and is an example of type III hypersensitivity (allergic) of Coombs and Gell. It is mediated by circulating immune complexes [12] and is not associated with alteration in cell-mediated immunity. It was originally described by Murata in Japan in 1912 [10].

ENH presents clinically as eruptive painful erythematous nodules (Fig. 5.17) and plaques over the entire body along and with systemic symptoms: fever, malaise, anorexia, pain, and joint swelling. The nodules, in severe reaction, may develop bullae, pustules, or necrosis [12]. Eventually fibrosis, scarring, and post-inflammatory hyperpigmentation develop [37]. Unlike erythema nodosum, which has a predilection for the shins, ENH may surface on extensor surfaces of both upper and lower extremities as well as on the face and trunk [37].

Severe ENH has systemic symptoms of fever and malaise and can manifest arthritis, dactylitis, uveitis, iridocyclitis, episcleritis, neuritis, lymphadenitis, myositis, adenitis, epididymitis, and orchitis [12]. On presentation patients may have anemia, neutrophilic leukocytosis, albuminuria, painful lymphadenopathy, glomerulonephritis, and hepatosplenomegaly [37]. Periostitis, especially over the tibia, may be detected on bone. Arthralgias and dactylitis may result and be confused with rheumatologic disease such as lupus erythematosus or seronegative rheumatoid arthritis [12, 37].

Fig. 5.17 Type 2 reaction (ENH)

Treatment of Reactions

The key to successful management of hanseniasis reaction is correct and early diagnosis and the timely initiation of anti-inflammatory measures (see Box 5.7). It is also important to remove the possible precipitating factors, and MDT should be continued at full dosage if the patient is receiving it. The most important

Box 5.7 Important note
Reactions dramatically worsen the clinical course of hanseniasis. They can occur before, during, or after MDT and can cause serious nerve impairment. They may constitute a medical emergency.

These reactions are often incorrectly viewed as adverse effects of MDT and are also confused with relapses.

goal of managing reactions includes preventing nerve function impairment.

Type 1 Reaction

- Prednisone 1 mg/kg/day provides rapid symptomatic relief and helps reverse nerve function impairment [5, 10, 12]. Symptoms should be reassessed every 2 weeks. If nerve function improves, the dose can be reduced by 5–10 mg. If there is no improvement or worsening of nerve function, the dose should be increased. Treatment may last up to 6 months or even years for those with neuritis. It is also possible to use prednisolone [4, 37], dexamethasone [5], or pulse therapy with methylprednisolone [5].

Long-term corticosteroid use carries the risk of adverse effects: hypertension, diabetes, osteoporosis, peptic ulcer, hematemesis, edema due to sodium retention, hypokalemia, moon face, and striae [10]. In Brazil there is a recommendation to treat *Strongyloides stercoralis* with thiabendazole or albendazole and to prevent osteoporosis by using calcium, vitamin D, and bisphosphonates [5].

- Other therapies include azathioprine (3 mg/kg/day) [12, 37], cyclosporine (5–10 mg/kg/day) [12, 37], methotrexate [12, 37], and mycophenolate mofetil [12]. In Brazil there is no guideline for the use of these drugs.

Type 2 Reaction

- Thalidomide 100–400 mg daily, depending on the severity of the ENH.

ENH is very responsive to thalidomide, which is available in Brazil [5] and the United States [12, 37]. Because of the well-known teratogenic side effects, the WHO does not support the use of thalidomide for the management of ENH in hanseniasis.

Thalidomide was first used for ENH in 1965, by Sheskin, in Israel, with excellent response against the reaction in the first 48–72 h [38]. In Brazil this drug was first used by Sampaio and Proença in the same year, and in 1971 the WHO published a bulletin confirming the efficacy of thalidomide in the management of hanseniasis-related EN [38].

Adverse effects of thalidomide include teratogenicity, sedation, peripheral neuropathy, dizziness, orthostatic hypotension, neutropenia, and hypersensitivity reactions. Male patients using thalidomide can excrete it in semen and must use a latex condom when having sexual contact with a woman of childbearing potential, and should not donate sperm [12].

- Prednisone 1 mg/kg/day is also effective and provides rapid relief when thalidomide is unavailable or cannot be used [5, 12, 37, 39]. It should be used together with thalidomide in severe ENH with the following manifestations: arthritis, dactylitis, uveitis, iridocyclitis, episcleritis, neuritis, lymphadenitis, myositis, adenitis, vasculitis, epididymitis, and orchitis.
- Pentoxifylline 400–1,200 mg/daily used alone or in combination with prednisolone for mild ENH [5, 39].
- Other treatments include nonsteroidal anti-inflammatory drugs, methotrexate, azathioprine [12, 37]. WHO guidelines for severe ENH suggest prednisolone, prednisolone and clofazimine, or only clofazimine (100–300 mg/daily) [39].

Relapse, Reactions, and Efficacy of MDT

The principal mode of assessing the efficacy of therapy for hanseniasis is the relapse rate, and there are wide variations in estimates of relapse rates after MDT in different regions [40]. The efficacy of MDT has been demonstrated by the extremely low relapse rate: 0.1% per year for paucibacillary hanseniasis and 0.06% per year for multibacillary hanseniasis. Moreover, clinical trials have established the efficacy of the individual drugs within MDT for the treatment of hanseniasis [41].

However, relapse can occur, the most important predisposing factors of which are presence of persister bacilli, monotherapy, inadequate or irregular therapy, and presence of multiple skin lesions and thickened nerves [40].

The conventional methods of confirming activity or relapse in an infectious disease (demonstration and culture of the etiologic agent) have limited utility in hanseniasis because of the difficulty in demonstrating bacilli in paucibacillary cases and absence of a method of in vitro cultivation of *M. leprae*. Bacteriologic parameters are useful in multibacillary hanseniasis, whereas in paucibacillary cases the criteria for relapse depend primarily on clinical features [40].

The most reliable criteria for making an accurate diagnosis of relapse include clinical, bacteriologic, and therapeutic criteria [41]. Relapse in multibacillary hanseniasis is defined as the multiplication of *M. leprae*, suggested by the marked increase (at least >twofold over the previous value) in the Bacteriologic Index at any single site, usually with evidence of clinical deterioration (new skin patches or nodules and nerve damage). This can be confirmed in most cases by clinical findings and the growth of *M. leprae* in the mouse footpad system [41].

Recognition of relapse in paucibacillary hanseniasis is somewhat difficult, as it is difficult to distinguish it from a reaction. In theory, a therapeutic test with corticosteroids may be able to distinguish between these two phenomena: definite improvement within 4 weeks of corticosteroid therapy denoting reaction, and nonresponse to corticosteroids during the same period favoring the diagnosis of clinical relapse. Definite evidence of clinical deterioration (new skin patches and/or new nerve damage) is sufficient to classify it as relapse in a paucibacillary case [41].

The main differential diagnoses for relapse are reversal reactions, ENH, and a specific group under increasing study that includes reactivation, resistance, and reinfection by *M. leprae* [40] (see Box 5.8).

> **Box 5.8 Important note**
> It is important to recognize and differentiate relapse from hansenic reaction because the therapeutics are different. Reactions are treated with anti-inflammatory drugs. Relapsed cases should be put back on MDT as soon as possible to prevent further disability and transmission of infection.

Systemic Involvement in Hanseniasis

Although the major manifestations of hanseniasis are seen in the skin and peripheral nerves, there are several other organs in the body that are invaded and affected by Hansen's bacilli (when the disease progress) and the immunologic changes (hansenic reactions) caused by its antigens (see Box 5.9).

In some organs the lesions are so severe that the functions of these organs are adversely affected. In most others, however, the involvement is so minimal that they usually go unnoticed [11].

In all forms of hanseniasis, bacteremia is present at some stage of the disease. In well-established multibacillary disease, while using MDT there is bacteremia, especially during the reactive phase. A number of *M. leprae* are sequestered in blood capillaries of various organs and, if they are lodged in a suitable environment, the disease process is initiated.

In the nose and upper respiratory tract, the anterior aspect of the eyes, testes, and lymph nodes with a temperature lower than that of the body, *M. leprae* proliferate to cause extensive and often severe lesions. Where the milieu is not suitable, the organisms evoke a mild reaction forming focal microgranulomas with no obvious organ dysfunction as happens in the liver, spleen, bone marrow, and adrenal glands. There are reports of finding occasional *M. leprae* in the endothelial cells of capillaries in the lungs, gastrointestinal system, and kidneys [11].

> **Box 5.9 Important note**
> The organs mainly involved are the nose, upper respiratory tract, mouth, tongue, palate, eyes, liver, spleen, lymph nodes, testes, kidneys, adrenal, bone, skeletal muscle, and breast in males.

Nerve Damage and Disabilities

If left untreated, hanseniasis can cause nerve damage, leading to muscle weakness and atrophy, and permanent physical disabilities and deformities appropriate to the disease [39]. Table 5.4

shows the WHO classification of deformities/disabilities in hanseniasis.

Currently there is no reliable information on the number of people affected at the global and country levels. It is estimated that globally there are around 2 million people with grade 2 disabilities attributed to Hanseniasis. Between 25,000 and 50,000 new people develop hanseniasis-related disabilities every day. These numbers would be higher if grade 1 disabilities were also included [13]. According to Yawalkar [10], it is estimated that approximately 25% of the patients who are not treated at an early stage of the disease develop anesthesia or deformities of the hands and feet.

The peripheral nerves consist of sensory, motor, and autonomic nerve fibers, damage to which results in anesthesia (loss of sensation), muscle weakness or paralysis, and lack of sweat and sebum, causing dry skin [10]. Damage to sensory fibers may result in abrasions, blisters, ulcers, burns, corns, callouses, and hematomas, with or without secondary infection of these primary lesions. Damage to motor fibers of the peripheral nerves may result in weakness and paralysis of the muscles supplied by the nerve, producing deformities such as claw hand, wrist drop, foot drop, claw toes, mask face, and lagophthalmos [10].

The nerve damage in hanseniasis can occur by either direct bacterial invasion or inflammatory response that develops during leprosy reaction, and can affect peripheral nerves of the face, arms, and legs. The common nerves affected in hanseniasis are the ophthalmic branch of the trigeminal, and the facial, ulnar, median, radial, lateral popliteal, and posterior tibial. The nerves are affected in approximately the following order of frequency: ulnar, posterior tibial, lateral popliteal, median, facial, and radial [10].

The common sites of nerve damage are [10]:

- Ulnar nerve: at the elbow, above the medial epicondyle of the humerus
- Median nerve: above the wrist joint
- Radial nerve: above the elbow joint, in the radial groove
- Lateral popliteal nerve: at the neck if the fibula
- Posterior tibial nerve: near the medial malleolus of the tibia
- Facial nerve: above the zygomatic arch (Figs. 5.18, 5.19, 5.20, and 5.21)

Fig. 5.18 Facial nerve damage: lagophthalmos

Table 5.4 The 3-grade WHO classification of deformities/disabilities in hanseniasis

Grade	Hands and feet	Eyes
Grade 0	No anesthesia	No eye problem due to hanseniasis
	No visible deformity or damage	No evidence of visual impairment
Grade 1	Anesthesia present	Eye problems due to hanseniasis are present, vision 6/60 or better, patient can count fingers at 6 m
	No visible deformity or damage	
Grade 2	Visible deformity or damage present: muscle atrophy of hands and feet, foot drop, wrist drop, claw hand, clawing of the toes, collapse of foot arches and plantar ulcers	Severe visual impairment (vision less than 6/60, the patient is unable to count fingers at 6 m), lagophthalmos, iridocyclitis, and corneal opacities

Adapted from WHO [13]

Fig. 5.19 Ulnar nerve damage: ulnar claw hand

Fig. 5.20 Radial nerve damage: wrist drop

Fig. 5.21 Posterior tibial nerve damage: plantar ulcers

Prevention of disabilities begins with diagnosing hanseniasis sufficiently early, recognizing and treating reactions and neuritis, identifying patients at risk of developing secondary disabilities, and intervening in time [13].

Contacts in Hanseniasis

The contacts of hanseniasis patients are known to have a higher risk of illness than the general population [4, 13, 42, 43]. Some authors report that household contacts of multibacillary patients presented a fourfold greater risk of becoming infected with the disease compared with noncontacts [43]. Having a current case of hanseniasis in the family is associated with a 2.9-times greater risk of a healthy family member becoming infected, and the risk increases when the family has a history of the disease. Children are exposed to the highest risk of becoming infected by being

in contact with a family member or anyone close to them who has the disease [12, 43], while anyone in household contact with a person with untreated multibacillary disease in an endemic area carries a 10% risk of eventually becoming ill, with children being at greater risk.

Contact surveillance therefore is an important strategy to ensure the early diagnosis and the control of this disease [44], and the examination of household and family contacts at the time of diagnosis and annually is recommended [12, 13].

The monitoring of contacts aims at the discovery of new cases among those who live or have lived with the patient diagnosed with hanseniasis (index case). In addition, surveillance aims to discover their potential sources of infection in the household (family) or outside (social, professional), regardless of whether the operational classification of the patient is paucibacillary or multibacillary [5, 42].

Household contact is considered as any person residing or who has resided with the hanseniasis patient [5, 43]. Anyone who lives or has lived with family or relations of the hanseniasis patient, closely and prolonged, is considered a social contact. Social contacts, including neighbors, coworkers, and schoolmates, among others, should be investigated in accordance with the grade and lifestyle, as should those who have had very close and extended contact with the untreated patient. Special attention should be given to family contacts of patients (parents, siblings, grandparents, uncles, etc.) [3].

The epidemiologic investigation of contacts consists of [3]:

- Anamnesis for signs and symptoms of hanseniasis
- Dermatologic and neurologic examination of all contacts of new cases, independent of the operational classification
- BCG (Bacillus Calmette–Guérin) vaccination for healthy contacts without presence of signs and symptoms of hanseniasis at the time of evaluation, whether contacts are paucibacillary or multibacillary cases (Table 5.5, see Box 5.10).

More recent guidelines recommend chemoprophylaxis with a single dose of rifampicin for

> **Box 5.10 Important note**
> All contact hanseniasis patients should be informed that the BCG vaccine is not specific to hanseniasis.

Table 5.5 Immunoprophylaxis with BCG

BCG scar	Conduct
No BCG scar	A dose
A BCG scar	A dose
Two scars BCG	Do not prescribe

Source: Brasil 2015 [42]

all identified contacts of an index case of hanseniasis. The chemoprophylaxis can be used as an additional intervention to reduce transmission of the disease. [6, 13, 42, 43].

The established treatment protocol consists of rifampicin 600 mg (2 tablets 300 mg) as a single dose [13, 42], to be administered in the second month of treatment of the index case (approximately 4 weeks after initiation of treatment of the index case). Children over 5 years of age are administered 450 mg rifampicin, and children or adults weighing less than 30 kg administered rifampicin 10–20 mg/kg [42].

Given the high risk of household contacts, it is important to examine the options available for preventing hanseniasis among contacts in some situations (see Box 5.11). Well-resourced programs and those detecting a significant number of new cases among household contacts may be able to consider immunoprophylaxis with BCG or chemoprophylaxis with a single dose of rifampicin for identified contacts. In addition, there is

> **Box 5.11 Important note**
> All household contacts of a new case of hanseniasis, regardless of whether paucibacillary or multibacillary, should be examined and followed for a period of 5 years after diagnosis of the index case.
>
> The surveillance of hanseniasis contacts is a priority action for control of the disease.

the question of ethics and confidentiality if some cases may not wish their diagnosis to be known to their contacts [13].

Glossary

ML Flow   Rapid test lateral flow to *M. leprae*. It is an immunochromatographic test strip comprising nitrocellulose with a detection reagent made of wool fiber with anti-human IgM antibody labeled with colloidal gold dried from one side, and an absorption strip on the other.

PGL-1 or phenolic glycolipid 1   The main antigenic glycolipid of Hansen's bacillus, the main antigenic determinant being the last part of di- and trisaccharide of the molecule. It is one of the first specific antigens isolated from *M. leprae*.

Ridley–Jopling classification   A classification of leprosy/hanseniasis for research purposes. This classification made by Ridley and Jopling was based on clinical, histologic, and immunologic differences in the disease, but they are continuous and compose a disease spectrum.

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Tuberculosis

6

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Key Points Summary

- Main factors involved in the increase of cases are HIV/AIDS, immunosuppressive drugs, multidrug resistance, and population migration
- Many types of clinical lesions are possible, such as inflammatory papules, verrucous plaques, suppurative nodules, and chronic ulcers
- The clinical presentation of the disease will depend on the route of infection, natural immune response, and the presence or absence of prior contact
- Endogenous cutaneous TB may occur by dissemination, contiguity, autoinoculation, lymphatic dissemination, and through hematogenous route. These include the scrofuloderma, orificial TB, lupus vulgaris, gumma TB, and acute miliary TB
- Tuberculids are hypersensitivity reactions to *M. tuberculosis* antigens, and include lichen scrofulosorum, papulonecrotic tuberculid, and erythema induratum of Bazin
- The classical tests include direct examination, culture, histopathology, and tuberculin skin test. New examinations include interferon-γ release assay (IGRA), polymerase chain reaction, and genotyping

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Introduction

Tuberculosis (TB) has become an endemic disease in developing countries, and is at risk of also becoming a problem in developed countries. There is one death because of TB every 15 (more than two million/year), and eight million people

develop TB each year. Up to 60% of people with the disease will die without treatment. Essentially the majority of the cases are in the Third World, reflecting the poverty and the lack of healthy living conditions and appropriate medical care [1–4]. The main factors involved in the increase of cases are acquired immune deficiency syndrome (AIDS) due to infection by the human immunodeficiency virus (HIV), the increased use of immunosuppressive drugs, the emergence of multidrug-resistant *Mycobacterium tuberculosis* (MTB), and population migration [1, 5–7].

The cutaneous infection by MTB follows the increase of pulmonary TB. It is difficult to notice the increase because cutaneous TB (CTB) is not one of the most frequent extrapulmonary forms, occurring in 1–2% of infected patients. CTB can occur by direct introduction of the microorganism into the skin, by hematogenous spread from an endogenous focus, or even by contiguity. The pathogenicity of the agent, the immune status of the host, and the presence or absence of sensitization to MTB influences the clinical presentation [7–11]. Therefore, many types of clinical lesions are possible, such as inflammatory papules, verrucous plaques, suppurative nodules, and chronic ulcers [12]. Histologically it is characterized by the presence of varying degrees of granulomatous inflammation, necrosis, and vasculitis. Observation of the bacillus is not always possible. The examination should then be complemented by others to the correct conclusion of the diagnosis [1, 13]. These complementary methods are used to improve diagnostic accuracy. Classical tests include direct examination, culture (gold standard), histopathology, and the tuberculin skin test (TST). More recently introduced examinations include interferon-γ release assay (IGRA), nucleic acid amplification test (polymerase chain reaction (PCR)), and genotyping. The classical tests are easy to perform and inexpensive but have low sensibility. The second are less operator dependent but are not familiar to many who deal with TB. Treatment is the same as for pulmonary

TB. However, it is necessary to make definitive assessment before starting treatment, conduct monitoring when using the medication, and be aware of bacterial resistance and how to manage such cases. This complexity makes knowledge of the subject vital for a proper approach to CTB therapy [1, 2, 7, 14].

Epidemiology

The global incidence of TB currently is around 133 per 100,000 inhabitants. Areas of low incidence have rates lower than 25 per 100,000 inhabitants. Regarding regional distribution, higher incidences exist in poor and underdeveloped countries. The incidence of TB per 100,000 habitants in 2014 was 28 in the American region, 48 in Europe, 116 in the Pacific region, 117 in the eastern Mediterranean region, 281 in Africa, and 286 in southwestern Asia. The incidence in the Americas is the lowest because it includes countries with very low rates, such as Canada [1]. Brazil shows an intermediate incidence, 44 per 100,000 inhabitants, in rates of mortality from the disease and in drug resistance [1], although the trend is one of improvement. In the past 17 years the incidence has decreased 38.7% and the mortality rate has decreased 33.6% [15]. Nevertheless, Brazil remains on the list of the 30 countries classified as high-burden areas, all of which may demonstrate one of the following situations: high incidence of TB, TB-HIV coinfection, and multidrug resistance to TB. Brazil is ranked in the burden list according to the absolute number of diagnosed cases of TB and TB-HIV coinfection. CTB constitutes about 1.5% of the total of all types of extrapulmonary TB. The involvement of other systemic organs in CTB, such as the lungs, bones, and abdomen, occurs in 35% of cases and should be actively investigated, as there are no statistics on CTB incidence. The prevalence in children ranges from 18% to 54% in India, with the majority of cases between 10 and 14 years of age [4, 5, 9, 16].

Etiopathogenesis

The genus *Mycobacterium* contains more than 174 species and 13 subspecies, including pathogenic, opportunistic, and nonpathogenic species, which are separated into three major groups: *M. tuberculosis* complex (MTC), *Mycobacterium leprae*, and mycobacteria other than MTC and *M. leprae*, referred to as nontuberculous mycobacteria (NTM). The MTC includes *M. tuberculosis*, *M. bovis*, *M. bovis* BCG, *M. africanum*, *M. caprae*, *M. microti*, *M. pinnipedi*, *M. canettii*, and *M. mungi*. The species of this complex are necessarily pathogenic and cannot survive in the environment for long periods, and therefore cause infection in humans and/or animals [5, 6, 17]. MTB, the most prominent member of the MTC, is the causative agent of TB. MTB is a Gram-positive, acid-fast bacillus (AFB). *M. bovis* has also been associated with the development of cutaneous lesions. MTB, which belongs to the *Shizomycetes* class, Actinomycetales order, Mycobacteriaceae family, and *Mycobacterium* genus, has about 4000 genes, most of which are involved in MTB survival or evasion mechanisms. MTB is able to develop and multiply both outside and inside phagocyte cells, being classified as a facultative intracellular parasite [5, 6, 17–20].

The immune response in TB occurs via the T-helper (Th) 1 pathway, with little or no involvement of Th2 pathway. Mycobacteria are inhaled and activate alveolar tissue macrophages. These phagocytose the infectious agents and trigger an intracellular apparatus to try to eliminate the bacillus [6, 8, 9, 11]. In trying to avoid death, MTB uses virulence factors, especially phagosome inhibitors, apoptosis inhibitors, and oxidative stress responders at this point [20]. If the mycobacteria survive they multiply inside the macrophages, thus inducing the production of cytokines for differentiation and recruitment of monocytes, lymphocytes, neutrophils, and dendritic and natural killer cells. They generate a cytokine production cycle which includes interferon-γ (IFN-γ), tumor necrosis factor α, interleukin (IL)-17, and IL-23. The chronic presence of these cytokines stimulates the macrophages to differentiate into epithelioid and giant cells and to organize themselves, to a greater or lesser extent, into granulomas [8–11].

Effectiveness in performing the containment leads to primary infection, latency, or cure [8, 9]. If MTB is not eliminated and remains inside the granuloma, it is associated with the possibility of immunosuppression, keeping the chance of relapse lifelong. CTB is mostly commonly secondary to a preexisting systemic primary focus in individuals incapable of forming and maintaining an efficient immune cellular response. The lesions may result from contiguity to the focus (orificial TB, scrofuloderma), hematogenous spread (acute miliary tuberculosis, tuberculous gumma, lupus vulgaris), or lymphatic dissemination (lupus vulgaris). The exceptions are tuberculous chancre and TB verrucosa cutis (TVC). Chancre occurs in individuals who have never had contact with MTB, and has pathophysiologic presentation similar to that of the first lung infection. The initial phagocytosis via mononuclear process occurs in the skin, and the presentation is in a local lymph node. TVC is secondary contact in an individual with good but remedially insufficient immune response [21–25].

Clinical Presentation

The clinical presentation of the disease depends on the route of infection, the quality of natural immune response, and the presence or absence of prior contact [7, 21]. This causes a geographic variation in clinical presentation according to the immunology of the affected population [21–25]. Inherent individual factors (age, sex, race) also influence the disease process. In children, possibly because of immature immunity, scrofuloderma and primary forms are more frequent. In adults, changes in immunological status, such as malnutrition, alcoholism, silicosis, diabetes, gastrectomy, and immunosuppressant conditions,

Table 6.1 Cutaneous tuberculosis classification

A. Exogenous cutaneous tuberculosis
(Tuberculous chancre and tuberculosis verrucosa cutis)
B. Endogenous cutaneous tuberculosis
(a) By contiguity or autoinoculation
(Scrofuloderma, orificial tuberculosis, and some cases of lupus vulgaris)
(b) By hematogenic and/or lymphatic dissemination
(Lupus vulgaris, tuberculous gumma or metastatic tuberculous abscess, and acute miliary tuberculosis)
C. Tuberculids (hypersensitivity reaction to MTB in patients with a high degree of tuberculin sensitivity)
(*Lichen scrofulosorum*, papulonecrotic tuberculid and *erythema induratum* of Bazin)
D. Cutaneous tuberculosis secondary to BCG vaccination

are important [26, 27]. CTB has a varied clinical and morphologic spectrum. CTB subtypes have been established based on three criteria: pathogenesis, clinical presentation, and histopathology [28]. The variants of CTB can be classified in several ways. The most commonly used is based on the inoculation mechanism [7, 12, 29] (Table 6.1).

The TB variants may also be divided according to the bacterial load of the skin: the multibacillar forms are those wherein the bacillus is easily detected in the cutaneous tissue or exudate isolated; the paucibacillary are those from which it is difficult to isolate the microorganism, with scattered bacilli or absence in histology. Multibacillar forms include tuberculous chancre, scrofuloderma, orificial TB, acute miliary TB, and metastatic tuberculous abscess. Paucibacillary forms are less common and involve TVC and lupus vulgaris (LV). In addition to these clinical forms, tuberculids, a category of skin disorders associated with TB, probably represent hypersensitivity immune reactions to *M. tuberculosis* antigens. This category includes three variants: the papulonecrotic tuberculid, lichen scrofulosorum, and erythema induratum of Bazin (EIB) [10, 26] (Tables 6.2 and 6.3).

Exogenous Cutaneous Tuberculosis

Exogenous inoculation of MTB may lead to tuberculous chancre, TVC, and more rarely to some cases of LV.

Tuberculous Chancre

This is a rare form of CTB, also called TB primary inoculation chancre, since it develops in individuals not previously sensitized by mycobacteria, occurring more often in children from endemic areas [12, 30]. Tuberculous chancre develops by direct inoculation of MTB in the skin or mucosa after local trauma often unnoticed by the patient. This inoculation can also occur with the use of inadequately sterilized needles, tattoos, circumcision, piercings, surgeries, and wounds. Face and extremities are the most commonly involved sites [7, 28, 31].

Generally 2–4 weeks after inoculation a papule or nodule appears that is firm, painless, and red-brown, and slowly develops into an ulcer. The ulcer is friable and prone to bleeding, and its base has a rough granular surface [32]. After 3–8 weeks from the onset of tuberculous chancre, there is often a spread of the bacillus through the lymphatics and lymph nodes, analogously to Gohn complex in the lungs [26]. Regional lymphadenopathy becomes evident and occasionally the lymph nodes drain into the skin. This phenomenon can have a sporotrichoid aspect [33]. Without treatment, tuberculous chancre may persist for more than a year. Evolution for spontaneous healing of 3–12 months can occur, leaving atrophic scarring and calcification in regional lymph nodes [30]. If treatment is not implemented there is a potential risk of complications, such as the hematogenous dissemination of the bacillus to other organs or acute miliary disease. Another possibility is development of LV, scrofuloderma, or verrucous plaque from the chancre [7].

Tuberculosis Verrucosa Cutis (TVC)

TVC is the most common form of exogenous CTB. The lesion develops due to direct inoculation in skin of previously sensitized individuals

Table 6.2 Etiopathogenic aspects of the forms of cutaneous tuberculosis

Clinical form	Inoculation route	Concentration of bacteria in the skin	PPD	Previous sensitization to mycobacteria
Tuberculous chancre	Exogenous	Multibacillary	Strong reactor	No
TB verrucosa cutis	Exogenous	Paucibacillary	Moderate to high reactor	Yes
Scrofuloderma	Endogenous by contiguity	Multibacillary	Strong reactor	Yes
Orificial TB	Endogenous by autoinoculation	Multibacillary	No reactor	Yes
Lupus vulgaris	Endogenous by hematogenic, lymphatic or contiguity	Paucibacillary	Strong reactor	Yes
Acute miliary TB	Endogenous by hematogenic	Multibacillary	No reactor	Yes
TB gumma	Endogenous by hematogenic	Multibacillary	No reactor	Yes
Tuberculids	Distant hypersensitivity	Absent	Strong reactor	Yes

Table 6.3 Clinical characteristics of CTB forms

Clinical form	Affected population	Prevailing cutaneous clinical aspect	Most affected anatomic area	Serious systemic impairment
Tuberculous chancre	Children and young individuals	Ulcer or verrucous plaque with regional lymphadenopathy	Face and extremities	No
TB verrucosa cutis	Children	Solitary hyperkeratotic verrucous plaques	Hands and feet	No
Scrofuloderma	Children, adolescents and the elderly	Cold, painless abscesses with fistulas	Face and neck	Possible
Orificial TB	Immunocompromised individuals	Erythematous to yellowish, painful and friable nodules and ulcers	Oral, nasal, anal, perineal or vulvar mucosa	Yes
Lupus vulgaris	Children and young individuals Women> men	Papules and well-defined, erythematous brownish plates with areas of hyperkeratosis and central atrophy	Face and neck	No
Acute miliary TB	Children and immunocompromised adults	Erythematous purplish papules, upon which small vesicles	Disseminated	Yes
TB gumma	Malnourished children and immunocompromised adults	Few floating subcutaneous nodular lesions that may ulcerate	Trunk and extremities	Yes
Lichen scrofulosorum	Children and young adults	Follicular or perifollicular erythematous brownish, asymptomatic, grouped and symmetrically distributed papules	Trunk and abdomen	No
Papulonecrotic tuberculid	Children and young individuals	Symmetric and recurrent eruption erythematous purplish, pustules and necrotic papules	Face, ears, extensor areas of the extremities and buttocks	No
Erythema induratum of Bazin	Young women	Subcutaneous nodules and erythematous purplish, slightly painful plates of 1–5 cm in diameter	Posterior surface of legs and thigh	No

with moderate to high immunity against MTB [7, 13, 27, 29]. These lesions are solitary, poorly symptomatic, and painless, and predominate in extremities such as fingers and feet [27, 28, 30, 34, 35]. The literature describes lesions in children's ankles or buttocks, due to contaminated soil with tuberculous sputum, but it is not commonly seen [10, 12]. In the past, professionals such as anatomists and medical doctors were prone to this type of CTB [30, 34]. The lesions begin as erythematous papules surrounded by a purpuric inflammatory halo, which evolves to an asymptomatic hyperkeratotic verrucous plate. The size varies from 1 to 5 cm in diameter [12]. The lesion grows centrifugally, sometimes accompanied by central atrophy [10, 30]. The plates are firm with verrucous surface and often exhibit cracks followed (or not) by purulent discharge. In general, regional lymphadenopathy is not present. More rarely, CTB can ulcerate or have an extensive multifocal presentation even in immunocompetent individuals [10, 36]. There are reports of psoriasiform, sporotrichoid, and keloid forms of CTB [36]. The purified protein derivative (PPD) of MTB is strongly positive. TVC may persist for many years if left untreated, although spontaneous resolution may occur [29, 30]. Secondary bacterial infection and elephantiasis are possible complications of extensive TVC that affects the extremities [10] (Figs. 6.1, 6.2, and 6.3).

Endogenous Cutaneous Tuberculosis

Endogenous cutaneous TB may occur by dissemination, contiguity, autoinoculation, lymphatic dissemination, and through a hematogenous route from another tuberculous focus. These include LV, scrofuloderma, gumma TB, acute miliary TB, and orificial TB.

By Contiguity or Autoinoculation

The adjacent structures transmit TB to the skin. Scrofuloderma, orificial tuberculosis, and LV arise from this process.

Fig. 6.1 TB verrucosa cutis

Fig. 6.2 TB verrucosa cutis

Scrofuloderma

Scrofuloderma, also known as tuberculosis colliquativa cutis, is the most common form of CTB in developing countries such as Brazil and India [37] and can occur at any age, although children, adolescents, and the elderly are the most affected

Fig. 6.3 TB verrucosa cutis

Fig. 6.4 Scrofuloderma

Fig. 6.5 Scrofuloderma

[13, 26]. Scrofuloderma arises from the secondary involvement of subjacent tuberculous focus, such as lymph nodes, bones, or testicular disease [7, 13, 34]. The presence of scrofuloderma already suggests systemic TB infection, particularly pulmonary disease [12, 28]. The occurrence of scrofuloderma after BCG vaccination has also been reported [38].

Cervical lymph node chains appear to be the major underlying source of subjacent infection with spread of disease to the facial skin and neck, although the armpits and groin but may also be affected. There is formation in the adjacent organ of cold painless abscesses, which fistulize with discharge of purulent secretion and caseous material [7, 10, 13, 28]. Lesions may be single or multiple. Following the evolution of the disease, ulcerated purpuric plaques and the development of multiple fistulas are observed (Figs. 6.4 and 6.5). Histopathology reveals tuberculous granulomas with caseous wedge-shaped necrosis. BAAR are easily seen in the cutaneous tissue or even upon direct examination of exudate. The TST is strongly positive [8]. Scrofuloderma tends to leave keloid scars, retractions, and atrophic sequelae. Spontaneous regression can occur, but it can take years for full resolution [12, 28].

Orificial Tuberculosis

Orificial TB, or tuberculosis cutis orificialis, is a rare manifestation of CTB that affects middle-aged adults and the elderly, with severe impairment of cellular immunity and advanced

pulmonary, intestinal, or genitourinary TB [32]. The lesions result from self-inoculation of viable mycobacteria in mucocutaneous tissue near body orifices [10, 13, 29]. Therefore the lesions affect the oral, nasal, anal, perineal, or vulvar mucosa [7, 13].

Clinically they appear as erythematous or yellowish papules or painful friable nodules, measuring from 1 to 3 cm in diameter, which can lead to painful ulcers with fibrinous base [10, 13, 27, 32]. Edema and inflammation are evident in perilesional tissue [30]. Culture for MTB is usually positive [8]. The TST is negative. There is no tendency to spontaneous regression [28]. Affected individuals have a poor prognosis, since there is severe underlying visceral disease and resistance to tuberculostatic treatment [13, 29]. If medication is not introduced, the lesions progress and contribute to the development of fatal disease [10].

By Hematogenic and/or Lymphatic Dissemination

Hematogenous and/or lymphatic dissemination from a primary focus of MTB infection may lead to LV, tuberculous gumma (metastatic tuberculous abscesses), and acute miliary TB.

Lupus Vulgaris

LV is considered by some authors the most common form of CTB in Europe and India [34, 39]. It can be acquired from endogenous infection (by hematogenous/lymphatic dissemination or by contiguity) and, more rarely, by exogenous inoculation of MTB or by BCG vaccination. It is a chronic, progressive, and potentially disfiguring form of CTB, which occurs in patients with a high degree of immunity against the bacillus [7, 27, 30]. It is very common in children and young people, this group accounting for 41–68% of cases of LV [28]. For unknown reasons, women are affected two to three times more often than men [29].

Clinical findings of LV are varied. It is most commonly characterized by papules and well-defined, erythematous brownish plaques, in facial and cervical areas, which rarely ulcerate [10]. In tropical countries, the development of lesions on

Fig. 6.6 Lupus vulgaris

the legs and buttocks is common [13]. The plaque grows peripherally, with serpiginous or verrucous borders, often reaching over 10 cm in diameter with central discoloration and atrophy. Diascopy of nonkeratotic areas reveals an "apple jelly" aspect. This feature is also seen in other granulomatous diseases, such as sarcoidosis and leprosy, and is rarely found in patients with black skin (Fig. 6.6) [10, 30]. Lesions do not always present the typical forms and are described as plaques, papules, and nodules, and vegetating, tumoriform, or ulcerated lesions. They mimic diseases, such as discoid lupus erythematosus, psoriasis, sporotrichosis, actinomycosis, and mycetoma [7, 40, 41]. LV can also develop into scrofuloderma drainage scar [8, 29, 42]. The culture of the lesion to mycobacteria is usually negative and the TST is positive [7]. Untreated LV lesions persist for years, gradually growing and leading to significant aesthetic alterations, with ulceration and tissue destruction [7, 10, 12, 30]. The incidence of malignant transformation into squamous cell carcinoma in LV ranges from 0.5% to 10.5%, and usually occurs after 25–30 years of untreated lesions [43, 44]. The development of other malignancies, such as basal cell carcinoma, has also been reported [27].

Tuberculous Gumma

Tuberculous gumma, also called metastatic tuberculous abscess, is a multibacillary CTB that results from the hematogenous dissemination of the bacillus by an active TB primary focus, especially in periods of decreased cellular immunity

[10, 30, 45]. Typically it affects malnourished children and immunocompromised adults, with rare reports in immunocompetent patients [10, 46]. Scrofuloderma and tuberculous abscesses have also been described in individuals with acute miliary TB [32, 46]. Usually there are few lesions, characterized by fluctuating subcutaneous nodules, which may ulcerate and drain caseous secretion (Figs. 6.7, 6.8, and 6.9) [30, 45]. Tuberculous gumma affects the trunk and extremities, and adenopathy is usually not present.

The TST can be positive or negative. Patients diagnosed with tuberculous gumma have a poor prognosis because of their compromised immunity and/or malnourishment. In immunocompetent individuals, abscesses may persist for years without treatment, and eventually resolve spontaneously [30].

Acute Miliary Tuberculosis

This is a rare and severe form of CTB resulting from hematogenous dissemination of the bacillus from the primary focus of TB, usually the pulmonary focus. Acute miliary TB typically affects

Fig. 6.7 TB gumma

Fig. 6.9 Metastatic tuberculous abscess

Fig. 6.8 Metastatic tuberculous abscess

individuals with impaired cellular immunity or severe immunosuppression. The patients have a negative TST, demonstrating absence of immune response against MTB [8, 10, 28]. This clinical form was first described in infants and children with reduced immunity after episodes of measles or scarlatina [28]. Although it is currently considered a rare form of CTB, the number of cases is increasing because of HIV, especially in CD4 counts of <100 cells/μl [47]. Acute miliary TB is systemic, presenting fever, anorexia, asthenia, and weight loss [8, 13]. It is important to note that most patients with this form do not have CTB. When present, the cutaneous lesions can be exanthema, small erythematous whitish papules, or erythematous purplish papules. The papules can evolve with vesicles, which subsequently break down, resulting in umbilication and crust formation [10]. They tend to regress in 1–4 weeks, leaving depressed and hypochromic scars [8].

Tuberculids

Tuberculids are considered hypersensitivity reactions to *M. tuberculosis* antigens present in extracutaneous focus or, rarely, after BCG vaccination. Such reactions occur in patients with moderate to high levels of immunity against the bacillus (tuberculin skin sensitivity) [8, 10, 12, 13]. Three disorders make up this group: lichen scrofulosorum, papulonecrotic tuberculid, and EIB. The pathogenesis of tuberculids has not yet been fully clarified. Some concepts support the classification of these three conditions as tuberculids: failure to detect MTB in the affected tissue reactions or cultures; the presence of extracutaneous infection by detectable MTB, with positive TST; histopathological evidence of granulomatous inflammation in skin lesions; and frequent resolution of cutaneous lesions with treatment against TB [10, 13].

Lichen Scrofulosorum

This is the rarest tuberculid, which affects children and young adults with lymph node or bone TB [10, 13, 30]. There are reports of lichen scrofulosorum emergence in young individuals and children after BCG vaccination or in *M. avium-intracellulare* complex (MAC) infection [49, 50]. Lichen scrofulosorum is characterized by asymptomatic hardened papules, reddish-yellow or red-brown color, sometimes brilliant, sized between 1 and 5 mm. They show a follicular or perifollicular distribution, symmetrically arranged in plaques most commonly observed in the trunk and abdomen of affected individuals [10, 12, 13, 30]. Necrotic lesions that leave hyperpigmented atrophic scars can be found in the topography of elbows, knees, legs, and extremities [28]. Bacilli are rarely found, although the DNA of the bacillus has already been identified in these lesions by PCR tests [48]. Without medication the lesions regress, without leaving scars, after months or years [29].

Papulonecrotic Tuberculid

This is the most common type of tuberculid, often observed in children and young people. It presents as symmetric and recurrent eruption of erythematous purplish papules that become pustular and necrotic, and affect most commonly extensor areas of the extremities and buttocks, but can reach the trunk and the face, associated or not with lymphadenitis [8, 10, 13]. Constitutional symptoms such as fever and asthenia may precede cutaneous manifestations [29]. Eruption may resolve spontaneously after weeks to months, resulting in formation of depressed varioliform scars (Figs. 6.10 and 6.11) [10, 13, 51]. Recurrences are common without tuberculostatic treatment, although when drugs are introduced, clinical improvement in days or a few weeks can be observed [52]. There are

Fig. 6.10 Papulonecrotic tuberculid

Fig. 6.11   Papulonecrotic tuberculid

Fig. 6.12   Erythema induratum of Bazin

reports of concomitant presentation of papulonecrotic tuberculid and EIB in the same patient [53, 54].

Erythema Induratum of Bazin

EIB is a granulomatous lobular panniculitis associated with TB, which affects the lower limbs of young and middle-aged women. It is a rare cutaneous manifestation of TB and has already been described even in patients with few symptoms or no underlying TB signal. Epidemiologic studies show that there is a greater predisposition in female patients, adolescents and young adults, patients with low phototypes or circulatory disorders of the lower limbs, and obese individuals [55]. It presents in the form of subcutaneous nodules and erythematous purplish plaques, measuring 1–5 cm in diameter, slightly painful, which persist for several weeks. They are usually distributed on the posterior surface of the legs and thighs [7, 55, 56]. Nodules can grow and reach a few centime-

ters in diameter [56, 57]. Central ulceration occurs in about 30% of EIB and are characterized by shallow, violaceous edges with a granular reddish base [58]. Lesions may regress even without treatment, after weeks to months, leaving depressed scarring and postinflammatory hyperpigmentation; however, recurrences may occur in outbreaks every 3–4 months [55] (Figs. 6.12 and 6.13).

The PPD and IGRA are frequently positive. The main clinical differential diagnosis is erythema nodosum (EN), characterized by the presence of nodular swelling and hardened, nonulcerative nodules seen predominantly in the lower limbs of women. It may be preceded by flu-like symptoms. EIB can be triggered by a variety of noninfectious and infectious agents. The disorder occurs via drugs and in association with systemic diseases, such as sarcoidosis and collagen diseases. Among infectious agents, streptococcal infection and primary TB are the most common etiologic factors. Histologically EIB is characterized by septal panniculitis without vasculitis. Other differential diagnoses include

Fig. 6.13 Erythema induratum of Bazin

cutaneous polyarteritis nodosa, pancreatic panniculitis, deep lupus erythematous, subcutaneous sarcoidosis, and cutaneous T-cell lymphoma [12, 55, 58].

Anti-TB treatment of EIB is recommended when TB is demonstrated. Most cases respond to antituberculous treatment [8]. When the association with TB is not detected, the term "nodular vasculitis" is used to refer to the manifestation of clinically and histologically similar panniculitis [57]. Hepatitis C, a potential trigger of nodular vasculitis, should be investigated when the possibility of TB is excluded [56].

Cutaneous Tuberculosis Secondary to BCG Vaccination

BCG vaccine (strain 1331) is a live mycobacteria vaccine derived from attenuated strains of *M. bovis*. It has been widely used to prevent serious TB infections, such as meningoencephalitis and acute miliary TB. However, it may cause skin complications such as tuberculids, LV, scrofuloderma, and outbreaks of TB in other organs, and nonspecific reactions, such as fever, local inflammation, abscesses, and regional lymphadenitis [7, 38, 59].

Complementary Examinations

Tuberculin Skin Test

The TST is a delayed hypersensitivity type IV reaction induced by T lymphocytes. The test identifies individuals who have had contact with MTB, identifies the antigens, with restriction or not of the bacillus, and develops immunological memory. For this reason, the test becomes positive only 2–10 weeks after contact with the bacillus [60, 61]. The TST technique consists in one injection of purified protein derivative (PPD) of MTB in the superficial dermis, in the middle third of the left forearm. If there is a problem in the skin, the right side of the left forearm can be used. The patient is instructed not to apply lotions or rub the injection site. After 48–72 h, the largest diameter of induration is measured with a millimeter ruler (Mantoux technique). If the patient does not attend, the maximum time allowed until the reading is 96 h [60] (Fig. 6.14).

There are two available derivatives, the PPD-RT 23 (Statens Serum Institute, Copenhagen) and the PPD-S (Tubersol-Aventis Pasteur, Toronto). Both use 0.1 ml in the test, but this volume corresponds to different amounts of units, two for the PPD-RT 23 and five for the PPD-S [60]. PPDs are not exclusive to MTB and therefore can produce false positives due to other mycobacteria or to vaccination, especially in the first 2–3 years [61, 62]. False-negative reactions can occur in cellular immunity alterations, such as age under 3 months or over 65 years, malnutrition, diabetes, kidney disease, pregnant women, recent severe infections, and congenital, acquired, or drug-induced immunodeficiency. Negative results also can occur by conservation or technical problems of application. The PPDs can degrade if the storage temperature is above

Fig. 6.14 Tuberculin skin test

8 °C or if exposed to radiation sources. The application errors include an insufficient amount of tuberculin, delay between the suction of the material and the application, too deep an injection, or misunderstanding of the result [60].

The TST result should be cautiously interpreted in the clinical context. It is important to provide the result in millimeters and avoid the classification of negative, weak, and strong reaction. For the correct interpretation of the test result it is necessary to evaluate the presence of the population vaccination status, the immunosuppression, and the bacterial load of the clinical presentation [63].

The vaccination brings some confounding factors. It increases the frequency of positive testing above 10 mm and increases the possibility of wrong diagnosis by latent TB due to endemic contact with MTB, leading to a decrease in TST sensitivity [10, 63].

Immunosuppression can decrease the size of TST induration and produce false negatives, even in smear-positive cases. For this reason, in this situation tests above 5 mm should be considered. Therefore it is vital to evaluate immunosuppressive factors such as HIV, medications, and diabetes in all patients. Assane et al. found 14.28% of HIV-positive patients in a series of 151 cases of CTB [64].

The clinical presentation of CTB is extremely important in TST result analysis. There is a relation between the bacillary load and the TST value in millimeters. Scrofuloderma and LV most frequently show strongly positive tests. Warty TB,

Table 6.4 Complementary examinations for CTB

A – Tuberculin skin test (TST)
B – Interferon-γ release assay – IGRA
(a) QuantiFERON® TB Gold In-Tube (QFT-G) test
(b) T-SPOT® TB test
C – Direct exam or bacilloscopy
D – Mycobacterial culture
E – Polymerase chain reaction (PCR)
(Conventional or in house PCR, real-time PCR, PCR with hybridization, PCR in situ, nested PCR, multiplex PCR)
F – Genotyping
(REA, PFGE, RFLP, spoligotyping, MIRU-VNTR)
G – Histopathological diagnosis
(a) Paucibacillary forms
(b) Intermediate forms
(c) Multibacillary forms

primary CTB, gumma TB, and tuberculids show wide variation in results, including low positive values. Acute miliary and orificial tuberculosis commonly deliver negative tests. To conclude, the result of the TST should be evaluated individually and in the clinical context. Tests with low positive values can be considered positives in the immunosuppressed and in presentations with low bacterial load [10, 61, 62]. Tests with high values may have low positive predictive value in the vaccinated population. The best practice is to complement the test with histopathologic and other laboratory techniques (Table 6.4).

Interferon-γ Release Assay (IGRA)

IGRA are tests used to identify indirectly a cellular immune response to specific peptides present in the MTB. Currently there are two commercially available tests approved by the US Food and Drug Administration, which use different techniques [10, 65]. The QuantiFERON TB Gold In-Tube (QFT-G) measures the IFN-γ produced by T cells in response to a protein cocktail, ESAT-6, SSN-10, and 7.7 TB. The test consists in a system of three tubes. The first contains the antigens, the second a mitogen to evaluate the cellular response (a positive control), and

the third an anticoagulant (negative control). In the negative control the IFN-γ produced before the test and unrelated to MTB is quantified. The blood is collected in the tubes and can be processed for up to 16 h. After the sample is incubated at 37 °C for 16–24 h and centrifuged, the plasma is removed and the IFN-γ is quantified by ELISA technique [66].

The test is positive if the IFN-γ measured in the tube with antigens is above 0.35 IU/ml and 25% higher than the value obtained in the negative control tube. If the IFN-γ is below 0.35 IU/ml or less than 25% of the negative control, the outcome depends on the positive and negative control tubes. If the negative is less than 8 and the positive is greater than 0.5 IU/ml at the same time, the result is negative. The cellular immune response works properly and there is no production of IFN-γ. If the negative control tube is greater than 8 or the positive control tube is less than 0.5 IU/ml, the result is indeterminate. The difference between the tube test and the negative control is too small and cannot be measured or the quantity/lymphocyte activity is low [65, 66].

The other test, the T-SPOT.TB, uses only two antigens separately. The mononuclear cells are separated, counted, washed, and then equally divided in four wells to avoid difference in the response between then. One well is the negative control, two wells contain antigens, one ESAT-6 (Panel A) and the other CFP10 (Panel B), and the last well is the positive control containing a polyclonal activator to confirm the functionality of mononuclear cells. After incubation, as ELISA is performed to detect the increase in the number of cells that secrete IFN-γ (number of spots present in the pit) [65, 67].

The test is positive if one of the test wells presents an increase of more than six spots relative to the negative control. A positive test is incontestable if there is an increase of more than 20 spots. An increase of between six and seven spots is borderline. The result is indeterminate if the negative control presents more than ten spots, regardless of the outcome of the test wells. In borderlines and indeterminate tests, standard practice is to retest with another technique. The test is negative if the antigen wells have not shown an increase in the number of spots or if the difference from the nega-tive control well is less than five spots [65, 67]. The antigens used in IGRAs are not present in the BCG and in the most part of other mycobacteria, with the exception of *M. kansasii, M. szulgai*, and *M. marinum*. This limits the false positives for these agents and eliminates the interference of BCG, resulting in fewer mistakes, especially in vaccinated populations [65]. The possibility of latent TB is the same as for the TST. A systematic review of 38 studies of pulmonary TB found a sensitivity average of 76% for the QFT-G and 90% for the T-SPOT.TB, regardless the vaccination. QFT-G presented 99% specificity in unvaccinated patients and 96% specificity in vaccinated patients, while the T-SPOT.TB presented 93% specificity in both groups [65]. There are few studies evaluating the test in CTB because of the low frequency of the disease. A prospective study of suspected cases of CTB using the T-SPOT.TB found sensitivity of 91.6%, very close to that of pulmonary TB, but lower specificity, 75.8%, mostly attributable to cutaneous atypical mycobacteriosis [68]. Despite the lower frequency of false positives, the method is not free from false negatives and indeterminate results. Risk groups are patients with a history of serious illness, prior hospitalization in intensive care, malnutrition, lymphopenia (especially when there is low CD4 count), an increase in C-reactive protein, a decrease in total protein levels, and aged older than 65 years. In this age group twice as many false negatives occur and 30% of the examinations have indeterminate results, while in other age groups this index is 3.1% [68–70]. The advantage is not limited to the issue of vaccination. It can also be applied in difficult situations to complete the diagnosis, such as latent TB screening, nephropathic or transplanted patients, children, immunosuppressed, tuberculids, and erythema nodosum. The few existing data reflect the difficulty of carrying out prospective comparative studies between IGRA and TST in patients with CTB [71–74].

Direct Examination or Bacilloscopy

Direct examination generally consists in searching for bacillus in a fresh sample stained with Ziehl–Neelsen staining acid. The bacilli appear

as reddish, isolated, grouped, or fragmented. Sterile conditions are necessary to remove the sample. The sample can be a scraping from an ulcerated lesion, a biopsy fragment, or secretion obtained from suppurative lesions. After collection, the material is placed in a sterile jar with saline solution. If it is a secretion, the material is distributed in a blade homogenizer before being put in the saline solution, which is kept between 2 and 8 °C and submitted for review within 24 h [73, 74]. The method presents low sensitivity because the presence of more than 5000 bacilli is necessary for it to be positive. Because of easy sample collection and higher bacterial load, it is more suitable for humid or suppurative lesions such as primary CTB, scrofuloderma, metastatic tuberculous abscess, or orificial tuberculosis [60, 61]. In a study of 95 cases of CTB, only two demonstrated positivity in a direct exam [75].

Mycobacterial Culture

Mycobacterial culture is the gold standard to determine the presence of active TB infection, and can also distinguish between the subspecies of mycobacteria and determine the sensitivity to antibiotics. The examination is necessary in all cases, especially in patients with previous contact with resistant TB or prior TB or leprosy treatment, in immunocompromised patients, and in the event of treatment failure [60, 61, 76]. In pulmonary TB culture, sensitivity is between 30% and 85%, compared with between 9% and 85% in CTB [75, 77–79]. A study found no difference in positivity between the clinical forms of CTB [80]. The test requires only between 10 and 100 bacilli to be positive, although the material selected, time until delivery to the laboratory, and culture medium are critical to the outcome [80]. Swab, direct aspiration, and biopsy are the methods used to collect the sample. Because culture of the biopsy fragment carries superior positivity to secretions, biopsy represents the specimen of choice. After local asepsis, the secretions and the necrotic tissues are withdrawn, and a 4-mm fragment in an area without necrosis or pus is removed and placed in a sterile jar with sterile physiologic solution. The patient's name and

the time of material collection are noted on the bottle. The material is delivered to the lab in less than 30 min, refrigerated, and protected from light [60].

The cultivation can occur in traditional medium (Lowenstein–Jansen or Ogawa–Kudoh) or radiometrically (automated or semi-automated). The latter increases positivity and reduces the waiting time for the result; however, as yet this method is not widely accessible or known by everyone. The dermatologist must remember to specify the culture to the mycobacteria in the request. The results take between 6 and 15 days, with the exception of Lowenstein–Jansen medium, which needs nearly 30 days [76].

Polymerase Chain Reaction

In this method the DNA present in fresh tissues, blood, or paraffin blocks confirms the presence of mycobacteria. The oligonucleotides (primers) delimit the beginning and the end of the desired DNA sequence. The DNA polymerase replicates the fragments, and the distribution of DNA bands in the agarose gel is compared with positive and negative controls. A single DNA sequence with varying sizes or multiple sequences at the same time (multiplex PCR) can be chosen. The sequences most commonly used for MTB are IS6110, IS986, MPB64, 65 kDa, and 38 kDa. IS6110 is considered the gold standard for MTC. It is a genetic element subject to translocation that is integrated in any location and any number in the chromosome, but is easier to find at some points (hot points) [81–84].

The waiting time for the result depends on the type of technique, ranging from 1.5 h for real-time PCR to 5 days for the conventional technique. The PCR techniques [81–84] are:

- **Conventional PCR or *in-house PCR***: standardized manual system by each laboratory. After the amplification, it is possible to sequence the fragment [72, 73].
- **Real-time quantitative PCR**: Automated PCR system. The selected fragment is associated with a fluorescent system to capture the light from the amplification, allowing imme-

diate knowledge of the result. The advantages over traditional amplification are rapidity, decreased contamination of material, and fewer errors in the process.

- **PCR with hybridization:** After the amplification, the fragments bind to a probe. A marker reacts with the probe, producing colors that can be identified and quantified by a spectrophotometer. This method Increases the chance of DNA detection and reduces false negatives.
- **PCR in situ:** The amplification occurs in the tissue, including paraffin blades, enabling demonstration of the location of mycobacterial DNA in the cell. Sensitivity is similar to that of traditional PCR. The positivity increases if in situ hybridization is added.

Few studies have reported statistical data on this method in CTB. Tan et al. described mean sensitivity of 73%. Addalla et al. analyzed 14 cases of CTB and atypical mycobacteriosis and found 88% sensitivity and 85% accuracy with PCR, superior to the TST and histopathologic examination (79% each) [80]. The positivity may vary with the bacillary load. Tan et al. analyzed the data according to the clinical form and found that PCR was 100% sensitive and specific in the immunocompromised with multibacillary forms. Meanwhile the mean sensitivity for LV, TB verrucosa cutis, and erythema induratum was about 56% [85]. Supporting this idea, Hsiao et al. described 56.2% sensitivity in paucibacillary forms. Furthermore, a retrospective study of archived paraffin blocks found only one positive result in 22 confirmed cases of CTB, demonstrating a loss of sensitivity to in situ PCR over time [86–88].

Genotyping

Genotyping employs molecular methods to identify specific DNA sequences or loci of MTB. This may include PCR at any stage of the process. Genotyping is useful for diagnostic confirmation, identification of resistance genes and clonality, and evaluation of strain dispersion

[88]. The main molecular typing methods are [5, 18, 85–88]:

(a) *REA* (restriction enzyme analysis of bacterial DNA): Digestion enzymes cut the DNA. The resulting fragments are separated and visualized by electrophoresis. The default obtained from each strain of bacteria is characteristic.

(b) *PFGE* (pulsed-field gel electrophoresis): Derived from the REA. Uses large fragments to eliminate the incorrect enzymatic digestion and, consequently, problems in the diffusion in the agarose gel. Good for atypical mycobacteriosis.

(c) *RFLP* (restriction fragment length polymorphism): The gold standard technique for genotyping in TB. Differences in the amount and location of IS6110 are used to identify the strain of MTB. The IS6110 is normally present in multiple copies in the DNA of MTB, a single copy on *M. bovis*, and absent in other mycobacteria. Is better for strains with high frequency of IS6110. Difficult to use for mycobacteria derived from culture.

(d) *AFLP* (amplified fragment length polymorphism): The DNA is cut by two different enzymes and is amplified with adapters. The fragments are visualized in polyacrylamide gel and read by autoradiography or fluorescence. AFLP is subject to methodologic flaws and is better for identification of atypical mycobacterioses than MTB, especially in differentiating *M. marinum* and *M. ulcerans,* which is very difficult using conventional methods.

(e) *Spoligotyping* (Spacer oligonucleotide typing): Identifies specific polymorphisms called DR (Direct Repeat). The locus DR is one of the hot spots for IS6110 integration to DNA. The loci resemble a necklace of beads (locus) with spaces between them (spacers). The strains are differentiated by the number of spacers identified. Cheaper and faster than RFLP, requires only the equivalent of two to three mycobacterial DNA and can use fresh samples, stained or from paraffin block. This increases the sensitivity of the method and makes it good for screening. Is very useful in

differentiating mycobacteria with low frequency of IS6110 (less than five copies), such as *M. bovis*.

(f) *MIRU-VNTR* (mycobacterial interspersed repetitive units–variable number of tandem repeats): Quantifies specific sequences called varied number of tandem repeats (VNTR) or mycobacterial interspersed repetitive units (MIRU). Very useful for identification of atypical mycobacteria such as *M. ulcerans* and *M. marinum*, and good for phylogenetic studies [5, 18, 88].

Histopathologic Diagnosis

All frames of CTB feature similar histological bases composed of lymphocytes, histiocytes, and epithelioid giant cells, organized in tuberculous granulomas [18]. The histologic differences observed for each clinical form reflect the organizational ability of the immune and control process of the bacilli in accordance with the individual ratio of Th1/Th2 response (Figs. 6.15, 6.16, and 6.17). This behavior, as noted by Sehgal et al., has histopathologic representation. Lymphocyte depletion, abundant bacilli, giant cells, and caseous necrosis indicate an inefficient cellular immunity, observed in the scrofuloderma; on the other hand, in LV, rare or no bacillus is observed, caseous necrosis is almost always absent, and granulomas are well formed, reflecting the ability to contain the infection. Meanwhile, the intermediate forms commute between these two poles, with variable and individual response [21, 89].

However, it is important to note that these are not two totally opposite poles, since if there are clinically apparent diseases, even in the spectrum of greater immunity, there is somehow a deficiency in cellular immunity, otherwise it would evolve to cure all forms of TB. At the same time the types with lower immunity have some degree of cellular response, because they are capable forming at least a granulomatous infiltrate. Didactically histology of CTB is divided into paucibacillary forms (well-formed granulomas and rare bacilli), intermediate forms (can migrate to both poles), and multibacillary forms (more inflammatory and rich in bacilli) [89–92].

Paucibacillary Forms

Lupus vulgaris: Epidermis may be atrophic (more rarely) or hypertrophic (more frequently), showing acanthosis and papillomatosis, even pseudoepitheliomatous hyperplasia. In the reticular
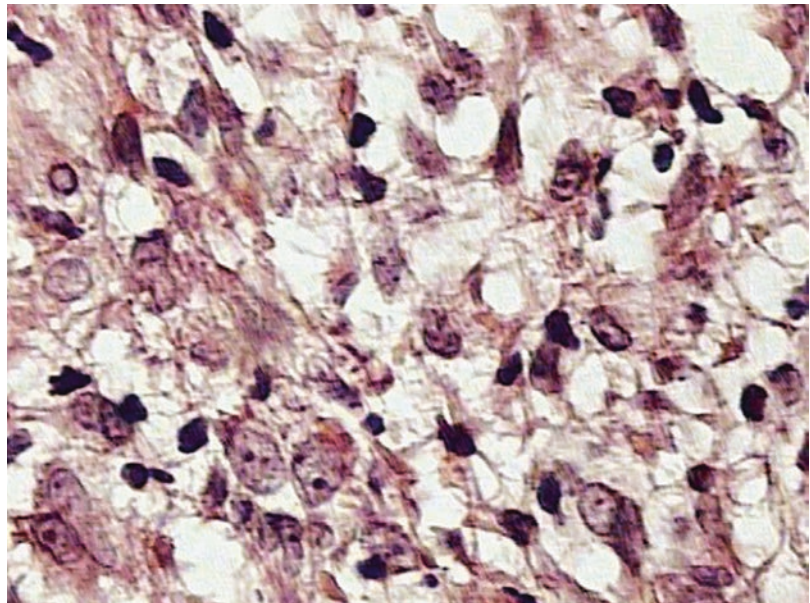
Fig. 6.15 Lymphocytes and epithelioid histiocytes in a granulomatous infiltrate

Fig. 6.16 Langhans giant cells are frequently found in the inflammatory infiltrate
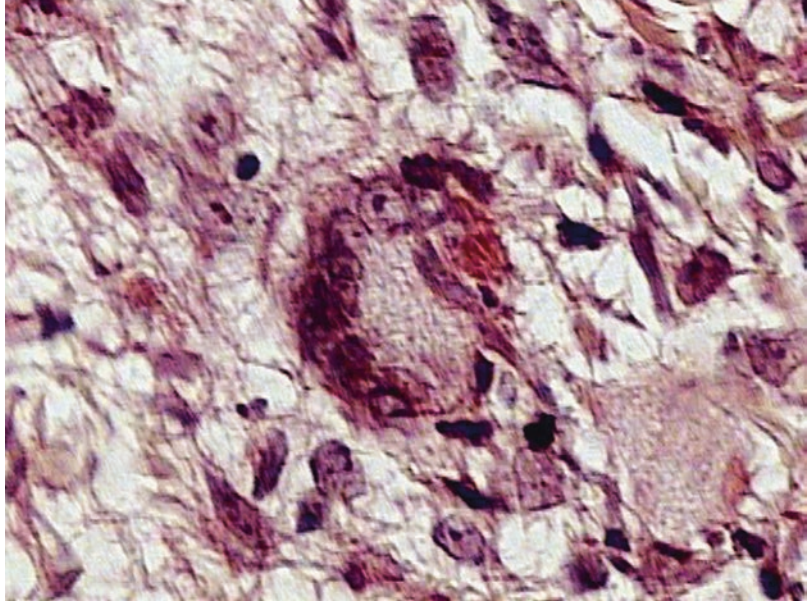
Fig. 6.17 Well-formed granulomas occupying the superficial and middle dermis
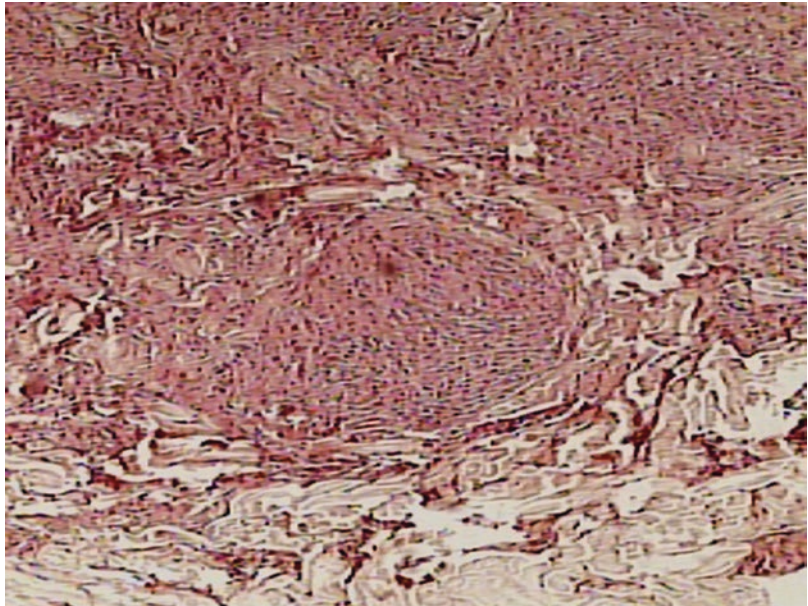
dermis there are well-formed tuberculoid granulomas with giant cells, Langhans type more frequently, or foreign-body type. Sarcoid-like granulomas may occur (Fig. 6.18). The lymphocytic infiltrate is dense and caseous necrosis is rarely present. If it occurs will be in small outbreaks, centrally to granuloma. Foreign body-type cells and fibrosis have been described. BAAR is infrequent [91, 92]. Note the that 8% of

cases can present with sarcoma, basal cell, or squamous cell carcinoma [93].

Lichen scrofulosorum: Epithelioid granulomas surrounded by lymphocytes and located more superficially in the dermis, adjacent to appendages. Despite the name, there is no lichenoid infiltrate. Normally, giant cells are absent. Caseous necrosis and BAAR are not found [94] (Fig. 6.19).

Fig. 6.18 Epidermic hyperplasia accompanied by granulomatous inflammatory process with noncaseaou necrosis foci in lupus vulgaris
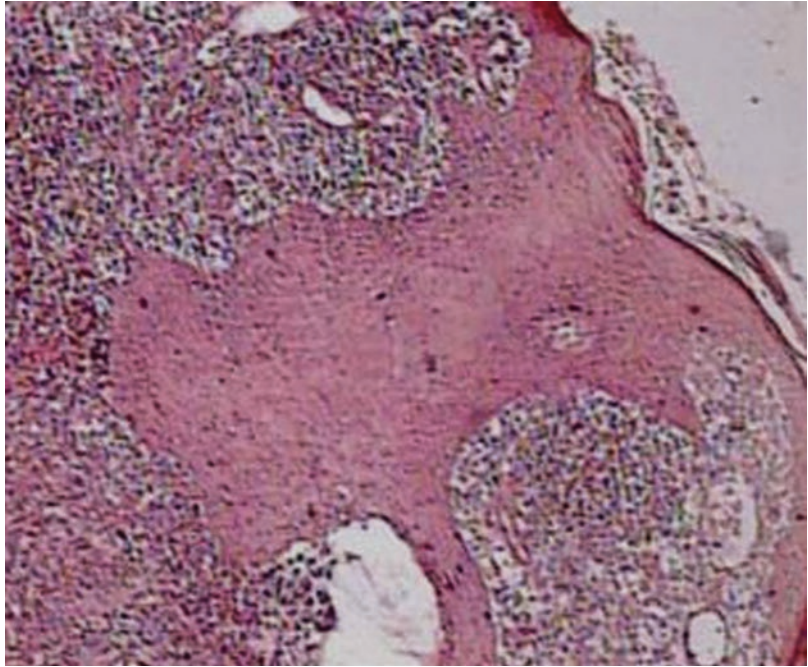
Fig. 6.19 Small granulomas distributed in superficial dermis in lichen scrofulosorum
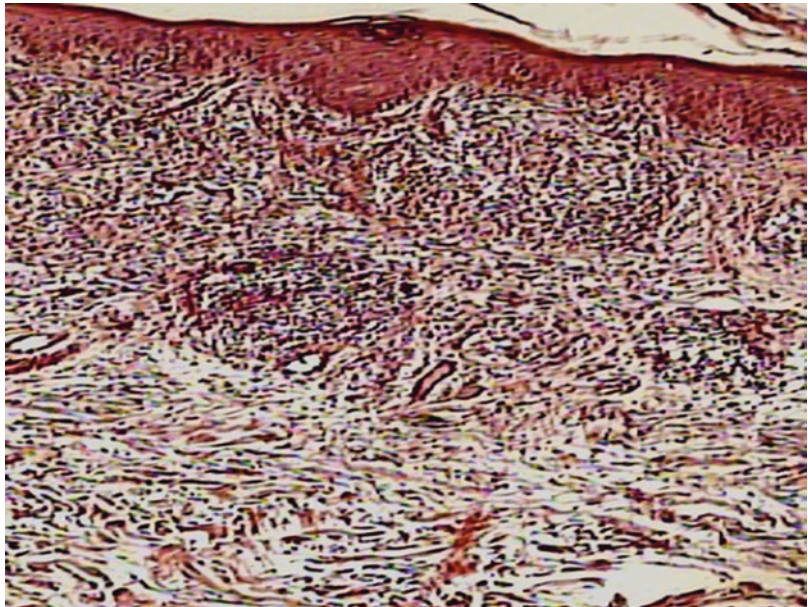
Tuberculosis verrucosa cutis: Marked by prominent alterations in epidermis such as hyperkeratosis, acanthosis, pseudoepitheliomatous hyperplasia, and papillomatosis. At the same time, in the middle dermis tuberculoid granulomas with microabscess or moderate-intensity caseous necrosis are seen. Bacilli are only rarely found [21] (Fig. 6.20).

EIB: Lobular panniculitis into the dermis, accompanied by vasculitis and foci of necrosis. Evolves to a granulomatous infiltrate over time, so the possibility of finding granulomas depends on the stage of the disease. Bacilli are not identified (Figs. 6.21, 6.22, 6.23, and 6.24) [92, 95].

Fig. 6.20 Tuberculoid granulomas with microabscess or moderate-intensity caseous necrosis in tuberculosis verrucosa cutis
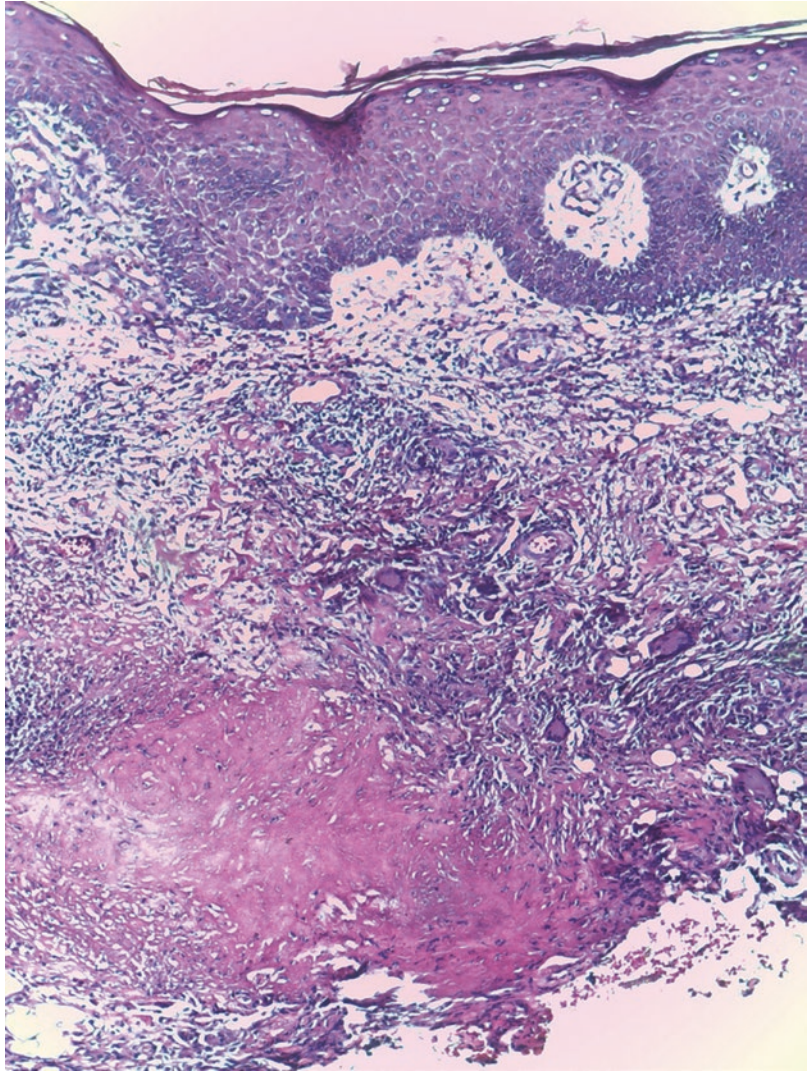
Fig. 6.21 Tuberculoid granuloma in Bazin's erythema induratum
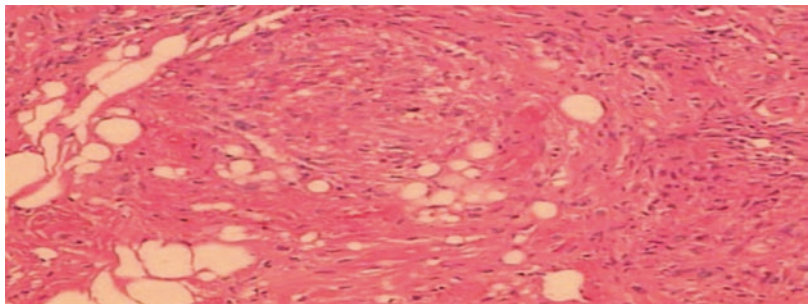
Fig. 6.22 Lobular panniculitis in Bazin's erythema induratum
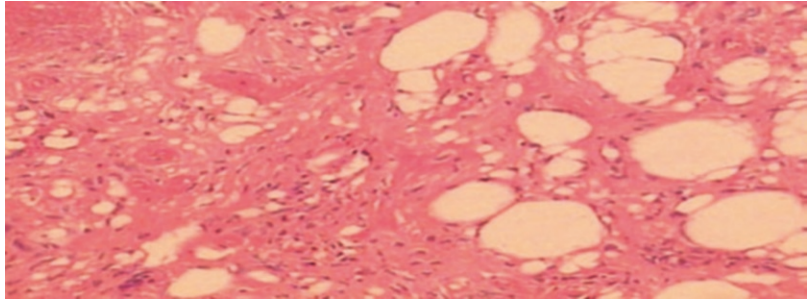
Fig. 6.23 Lobular panniculitis in Bazin's erythema induratum
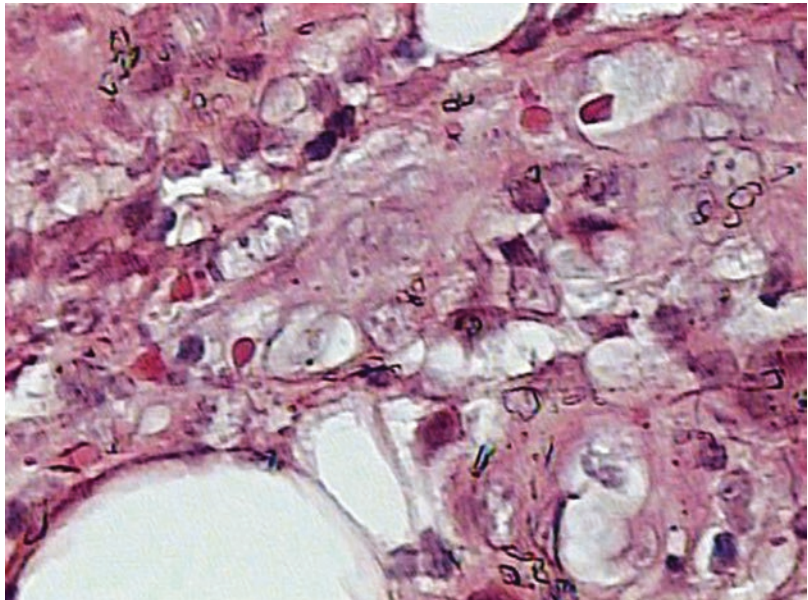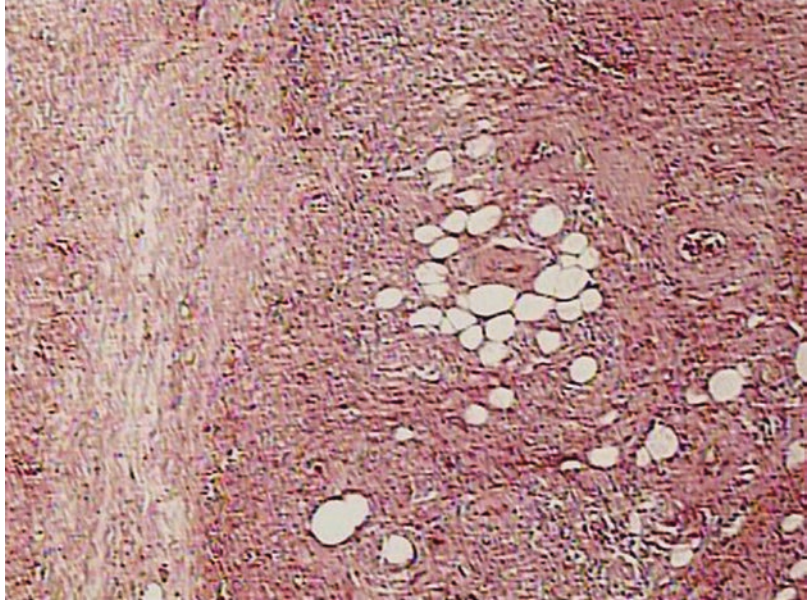
Fig. 6.24 Detail of the fat lobule surrounded by the infiltrate in Bazin's erythema induratum

Papulonecrotic tuberculid: Found in descending order of frequency: dermal-epidermal necrosis, granulomatous infiltrate, leukocytoclastic vasculitis, perivascular edema or necrosis, and follicular suppuration. BAAR in general are not identified [96].

Intermediate Forms

Primary tuberculosis: Histopathology varies with time from inoculation. The initial histopathology shows an acute neutrophilic inflammatory reaction, rich in BAAR and necrotic areas. After 4–6 weeks, there are caseous granulomas and the number of bacilli decreases [8, 61].

Multibacillary Forms

Scrofuloderma: Massive central caseous necrosis in the superficial dermis with abscess formation and macroscopic suppuration in many cases. On the periphery of the lesion, tuberculous granulomas occupy the entire dermis. When present, MTB can also be found in this location [61, 92] (Fig. 6.25).

Orificial tuberculosis: On the middle-deep dermis, there is a granulomatous infiltrate accompanied by focus of caseous necrosis distributed around a central and superficial ulcer. Bacilli can be identified near the infiltrate [61, 97].

Metastatic tuberculous abscesses and gumma: Central ulceration with caseous necrosis, surrounded by a crown of giant cells and macrophages. BAAR are often found [98].

Acute miliary tuberculosis: Nonspecific inflammatory infiltrate rich in lymphocytes and plasma cells. If there is caseous necrosis, this is focal and occasionally microabscesses are observed. Bacilli are usually present [99].

The histopathologic examination is crucial in the investigation of CTB and the identification of the agent is essential to conclude the diagnosis. However, in practice many cases feature great difficulty because the bacillus is not found even with special stains [25]. The bacillus is identified in from zero to 13% of histologic examinations [25, 75, 77–79, 100–103]. Only one study identified the bacillus in 50% of the examinations [102]. Among the clinical forms, the inflammatory are those in which the MTB is most commonly found, such as scrofuloderma and orificial TB [102, 103]. Regarding the histologic elements classically described in CTB, the tuberculous granulomas are the most frequently found, in between 57% and 96% of cases [25, 77–79, 100–103]. In sequence, there are the epidermal hyperplasia and caseous necrosis, ranging from 57% to
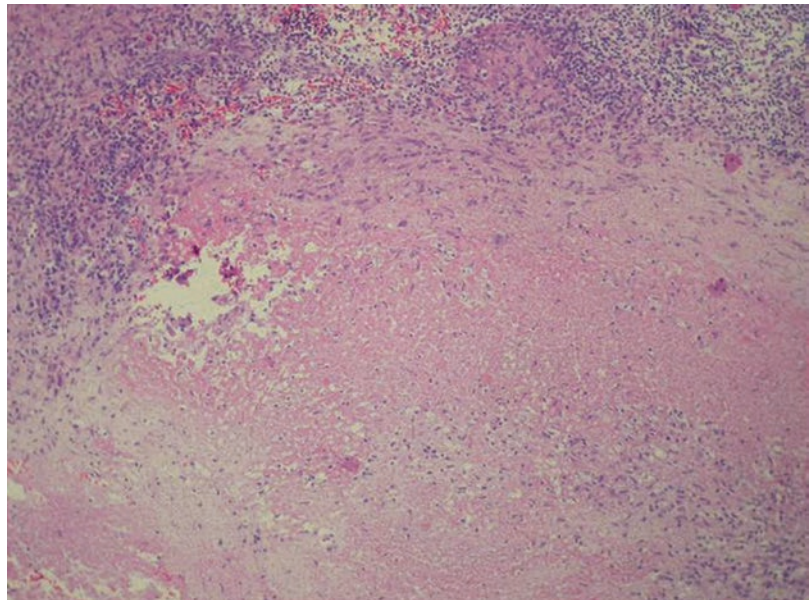
Fig. 6.25 Extensive caseous necrosis surrounded by a granulomatous process in scrofuloderma

Table 6.5 Comparative histologic studies of CTB and other infectious granulomatous diseases

Authors		Conclusions
Paksoy and Hekim Turkey, 1993	Lupus vulgaris versus cutaneous leishmaniasis	Giant cell granulomas are more frequent in TB
Nirmala et al. India, 1977	CTB versus tuberculoid leprosy	In CTB epidermal hyperplasia more frequently, small areas of ulceration, significant fibrosis, and caseous necrosis
Min et al. South Korea, 2012	CTB versus atypical mycobacteriosis	Giant cell granulomas and caseous necrosis were associated with CTB ($p < 0.05$)

86% [25, 77, 100, 103] and from 12% to 57%, respectively [25, 77, 100, 103]. The first is more frequent in the verrucous forms and the second in the inflammatory forms [77, 101, 103]. In 11–20% of the samples of confirmed CTB cases it is not possible to predict the diagnosis from the histology [77, 102, 103]. In addition, the CTB can present with atypical granulomas similar to yeast infections (mixed infiltration with suppuration), granuloma annulare, rheumatoid nodules, and sarcoidosis [103, 104].

Some studies tried to find elements that could differentiate CTB from diseases with similar histology [105–107]. Min et al. compared CTB with atypical mycobacteriosis and found the presence of neutrophils, interstitial granuloma, vascular proliferation, and a high number of bacilli were associated ($p < 0.05$) with the atypical mycobacteriosis, while giant cell granulomas and necrosis were associated with CTB also to a significant degree ($p < 0.05$) (Table 6.5). Unfortunately, the analysis is limited to the diseases studied and it is not possible to generalize these results to other diseases [105].

Differential Diagnosis

Several infectious diseases, as well as some tumor and inflammatory diseases, can simulate CTB. The correct survey of hypotheses should take into account the patient's age, clinical presentation, and anatomical location (Table 6.6).

Therapeutic Approach

TB treatment takes into account the age and weight of the patient, and lasts 6 months, regardless of TB form. The exception is meningoencephalitis, whose treatment lasts 9 months. In patients with HIV, treatment may be extended to 9 months based on the medical criteria. The treatment consists of two stages, a 2-month intensive phase and a 4-month maintenance phase. Patients under 10 years use three drugs in the intensive phase: rifampicin, isoniazid, and pyrazinamide (2RHZ). Patients older than 10 years use four drugs: rifampicin, isoniazid, pyrazinamide, and ethambutol (2RHZE). Both use two drugs for 4 months in the maintenance phase: rifampicin and isoniazid (4RH) (Tables 6.7 and 6.8). The medications should be taken together, preferably on an empty stomach, 1 h before or 2 h after breakfast or, in the case of digestive intolerance, with a meal [60, 108, 109].

The drug association, correct intake, and time indicated should be enough to cure virtually 100% of cases of TB. However, factors such as dose abstention, incorrect dose, nonstandard hours, breaks in treatment, monotherapy, and abandonment of treatment induce bacterial resistance to antibiotics and lead to more intensive care in the follow-up [27, 60].

Before starting treatment an active search should be conducted for other TB outbreaks. The involvement of other organs associated with CTB is described in between 4% and 35% of cases, the lung being the most affected organ. The identification of lesions in other organs contributes to increasing the material subjected to culture, aiding in monitoring the response to treatment and the correct indication of treatment time. The physical examination should include pulmonary evaluation, joints, and palpation of lymph node chains. If any lymph node is suspected, puncture and culture should be requested. In addition to chest X-ray, the examinations include direct examination and culture of the sputum with antibiogram and urinalysis (aseptic leukocyturia) with culture for acid-fast bacilli. Specific examinations, such as abdominal ultrasonography, excretory urography, and cranial, soft tissue, or

Table 6.6 Differential diagnosis of clinical forms

Clinical form	Differential diagnosis
Scrofuloderma	Pilonidal cysts, branchial cyst (in children), suppurative hidradenitis (Hurley 1), lymphogranuloma venereum, septic arthritis, cervical abscess, squamous cell carcinoma (SCC) of oropharynx
Nodular abscedens lesions	
Lupus vulgaris	
(Plates with live erythema, desquamation, and infiltration of varying degrees)	Hemangioma, psoriasis, rosacea, granulomatous chromoblastomycosis, erysipeloid, subacute cutaneous lupus erythematous
TB verrucosa cutis	
(Well-defined plates with hyperkeratosis of varying degrees)	Verrucous lupus erythematosus, chromoblastomycosis, SCC, verrucous leishmaniasis, wart verruca, pseudoanhum, chronic eczema
Acute miliary TB	
(Erythematous brownish small papules or pustules)	Secondary syphilis, cutaneous histoplasmosis, PLEVA
Gumma TB	
(Floating subcutaneous nodules)	Syphilitic gum, sporotrichosis, furuncle, phaeohyphomycosis
Primary tuberculosis	
(Initial phase: subcutaneous tissue inflammation)	Initial phase: bacterial or fungal mycetomas, cellulitis, *M. marinum*
(Chancre stage: ulcer of well-defined edges)	Chancre stage: leishmaniasis, chancroid, paracoccidioidomycosis, pyogenic granuloma
Orificial TB	
(Papules, nodules, and ulcers friable in semimucous)	Hidradenitis suppurative (Hurley 2–3), Crohn's disease or rectocolitis, anal fistula, mucocutaneous paracoccidioidomycosis, ulcerated hemorrhoid, Bowen's disease
Erythema induratum of Bazin	
(Infiltrated erythematous purplish plaques with areas of necrosis and suppuration)	Medium vessel vasculitis, chemical panniculitis, superficial thrombophlebitis, glomerulonephritis, subcutaneous T-cell lymphoma
Lichen scrofulosum	
(Erythematous brownish small papules, somewhat scaly)	Granuloma annulare, erythema annulare centrifugum, confluent and reticulated papillomatosis of Gougerot and Carteau, psoriasiform subacute lupus erythematous, psoriasis, lichen planus annularis
Papulonecrotic tuberculid	
(Firm papules of varying size with central small crust, tending to symmetric distribution)	Cryptococcosis, Behçet's disease, insect bite hypersensitivity

Table 6.7 Basic scheme for the treatment of TB in adults and adolescents

Scheme	Medication	Weight range (kg)	Unit/dose	Time period
2RHZE Intensive phase	RHZE 150/75/400/275 mg In fixed-dose combination tablet or capsule	20–35	2 tablets or capsules	2 months
		36–50	3 tablets or capsules	
		>50	4 tablets or capsules	
4RH Maintenance phase	RH 300/200 mg or 150/100 mg capsule or tablet	20–35	1 tablet or capsule 300/200 mg	4 months
		36–50	1 tablet or capsule of 300/200 mg + 1 comp or capsule of 150/100 mg	
		>50	2 tablets or capsules of 300/200 mg	

R rifampicin, *H* isoniazid, *Z* pyrazinamide, *E* ethambutol

Table 6.8 Basic scheme for the treatment of TB in adults and adolescents

Scheme	Medication	Weight of the patient			
		Up to 20 kg > mg/kg/day	20–35 kg mg/kg/day	35–45 kg mg/kg/day	>45 kg mg/kg/day
2RHZ Attack phase	R	10	300	450	600
	H	10	200	300	400
	Z	35	1000	1500	2000
4 RH + Maintenance phase	R	10	300	450	600
	H	10	200	300	400

joints magnetic resonance imaging (MRI), are requested according to symptoms and the first test results [78, 79, 101].

The initial evaluation also includes laboratory tests to assess the health condition of the patient, contraindications and adjustments in medication; complete blood count, liver enzymes, renal function, and uric acid. With the introduction of ethambutol in the default schema, patients must undergo ophthalmologic evaluation due to the risk of optic neuritis, more often when use of the drug extends to more than 2 months. The follow-up should be monthly to assess symptoms of adverse reactions to drugs, the presence of jaundice or rash, the evolution of cutaneous lesion and other foci if they exist, and the general laboratory and the sputum culture. The smear should be negative in the second month of treatment [60]. The patient should be asked about experience of gastric intolerance, change in urine color, burning sensation in the feet, arthralgia, myalgia, pain in oropharynx, alteration of visual acuity, or color perception. If using streptomycin, the patient should also be questioned about pain at the injection site and tinnitus [27].

Analogous to the pulmonary bacilloscopy, in most cases it is possible to notice an improvement in cutaneous lesions, decrease in lesion size, wound healing, and even clinical cure in the first 2 months of treatment [64, 77]. In 6 months about 81–100% of cases are cured. However, some authors report that about 8–15% of cases only showed healing after 8–24 months of treatment [64, 77, 101]. In the cases with slow response to treatment or not healing at the end of the standard time period, the possibility of bacterial resistance, atypical mycobacteriosis, and transformation in indolent tumors, especially in LV, should always

Table 6.9 Conduct front of mono- and multiresistance

Drug resistance	Intensive phase	Maintenance phase
Isoniazid	2 months ago RZES	4 months RE
Rifampicin	2 months HZES[a]	10 months EH
Isoniazid and pyrazinamide	2 months RESO[b]	7 months REO
Isoniazid and ethambutol	2 months RZSO[b]	7 months RO
Rifampicin and pyrazinamide	3 months HESO[a,b]	9 months HEO
Rifampicin and ethambutol	3 months HZSO[a,b]	12 months HO
Isoniazid, pyrazinamide, and ethambutol	3 months RSOT[a,b]	12 months ROT

R rifampicin, *H* isoniazid, *Z* pyrazinamide, *E* ethambutol, *S* streptomycin, *O* ofloxacin, *T* terizidona

[a]The streptomycin may be replaced by a fluoroquinolone, which should be used in the two phases

[b]The levofloxacin can substitute the ofloxacin. The intensive phase can be extended to 6 months

be remembered [93, 110]. Acute miliary tuberculosis currently has the highest reported resistance [99], but there are reports of resistance to scrofuloderma and LV [110].

In these situations, a new biopsy should be done with a request for culture and antibiogram or genotyping. If in the first 2 months of treatment no improvement is observed, in addition to the biopsy the therapeutic scheme should be replaced (Table 6.9). In the situation of slow but progressive improvement, treatment can be extended to 9 months. If the injury persists after that time, the drug schema should be changed. If the culture is negative or it is not possible to perform genotyping for resistance, the change should be discussed with a doctor experienced in treating TB [60, 110, 111].

It is important to note that clinical cure does not indicate microbiological cure, and the treatment should be continued for 2 months after complete resolution of the lesion [27]. After the end of treatment the patient should undergo regular follow-up and be instructed to return to monitor changes in scarring. Recurrences are uncommon, but are reported by some authors [64, 77].

Surgical Treatment

Surgical treatment is not indicated routinely, but can be considered in cases of therapeutic failure, small injury, and absence of disease in other organs. Surgery must be combined with drug treatment [110, 111].

Special Circumstances [60, 111]

Pregnancy

In pregnant women the standard treatment should be performed normally because there is no evidence of teratogenic effects of rifampicin, isoniazid, pyrazinamide, and ethambutol. In pregnant women using isoniazid, pyridoxine (50 mg/day) routinely is added to avoid peripheral neuritis and prevention of convulsion in newborn. Women currently breastfeeding should be directed to undergo the treatment because of the low concentration of these drugs in breast milk, but while paying attention to adverse effects. If there is a need for an alternative scheme streptomycin, ethionamide, and quinolones may be used. The agents ofloxacin, capreomycin, clarithromycin, clofazimine, and paraminosalicylic acid should have the benefit-risk evaluated before being recommended.

Elderly

The treatment is the same while adjusting the dose according to the weight. Remember that the elderly have increased frequency of adverse effects due to metabolic changes and polypharmacy.

Kidney Disease

The range or the drug dose should be adjusted in patients with creatinine clearance under 30 mL/min. If the clearance of creatinine is >30 mL/min, the standard dose should be used whenever possible with monitoring of serum levels.

Liver Disease

The medications used in the treatment for TB entail the risk of hepatotoxicity. In the first 2 months of treatment transient elevation of liver enzymes can occur. In patients without prior liver disease or liver disease without cirrhosis, treatment should be discontinued if the patient has jaundice or enzyme values three times above the normal value. If the enzymes normalize, medications must be returned in the following order: rifampicin + ethambutol, followed by isoniazid, and finally, pyrazinamide, with a 3- to 7-day interval between them.

In patients with prior liver disease with cirrhosis, enzymes persistently higher after 4 weeks of treatment, or if they rise again after re-introduction of the treatment, the schema must be changed to 3 months on streptomycin, ethambutol, and ofloxacin, followed by 9 months of ethambutol and ofloxacin.

Glossary

Acid-fast bacilli (AFB)   testing may be used to detect several different types of acid-fast bacilli, but it is most commonly used to identify an active tuberculosis infection caused by the most medically important AFB, *Mycobacterium tuberculosis*. Are called acid-fast bacilli because they are rod-shaped bacteria (bacilli) that can be seen under the microscope following a staining procedure whereby the bacteria retain the color of the stain after an acid wash (acid-fast).

Bacille Calmette-Guérin   Vaccine (strain 1331) is a live mycobacteria vaccine derived from attenuated strains of *Mycobacterium bovis* to prevent tuberculosis and other mycobacterial

infections. BCG has been recommended only for immune-competent children and adults who have high risk of ongoing exposure that cannot be avoided. In addition, it is used as an immuno-stimulant in the treatment of several diseases.

Erythema induratum of Bazin (EIB) Is a granulomatous lobular panniculitis associated with tuberculosis, which affects the lower limbs of young and middle-aged women.

Erythema nodosum Is characterized by the presence of nodular swelling, hardened, non-ulcerative nodules which are seen predominantly in the lower limbs of women.

Lupus vulgaris Is a chronic, progressive, and potentially disfiguring form of cutaneous tuberculosis, which occurs in patients with a high degree of immunity against *Mycobacterium tuberculosis*.

Tuberculin skin test (PPD, Mantoux technique, TB skin test) technique consists in one injection of purified protein derivative (PPD) of *Mycobacterium tuberculosis* in the superficial dermis, in the middle third of the left forearm. The TST is a delayed hypersensitivity type IV reaction induced by T lymphocytes.

Tuberculous gumma Also called metastatic tuberculous abscess, is a multibacillary cutaneous tuberculosis. It results from the hematogenous dissemination of the bacillus by an active tuberculosis primary focus, especially in periods of decreased cellular immunity.

Tuberculosis verrucosa cutis Is the most common form of exogenous cutaneous tuberculosis. The lesion develops from direct inoculation in the skin of previously sensitized individuals with moderate to high immunity against *Mycobacterium tuberculosis*.

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Other Mycobacterioses

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Key Points Summary

- Nontuberculous mycobacteria (NTM) are generally considered to be environmental saprophytes
- *Mycobacterium fortuitum* is the most common of the rapidly growing mycobacteria (RGM) encountered in clinical practice
- *Mycobacterium ulcerans* is a slow-growing acid-fast bacillus that causes a cutaneous infection known as Buruli ulcer
- The *M. fortuitum* group is responsible for 60% of community-acquired localized cutaneous infection cause by RGM
- *Mycobacterium avium-intracellulare* complex is the most frequent bacterial opportunistic infection in persons with HIV/AIDS

Introduction

Mycobacterioses are infections caused by bacteria of the genus *Mycobacterium*, rod-shaped aerobic or microaerophilic bacteria that are Gram-positive, acid-fast members of the order Actinomycetales and family Mycobacteriaceae. They are spread throughout the environment, particularly in water reservoirs. The genus *Mycobacterium* contains more than 174 species and 13 subspecies, including pathogenic, opportunistic, and nonpathogenic species, which are separated into three major groups, *M. tuberculosis* complex (MTC), *M. leprae*, and mycobacteria other than MTC and *M. leprae*, collectively referred to as nontuberculous mycobacteria (NTM). NTM are acid-fast bacilli (AFB) commonly found in potable water. NTM include both saprophytic and opportunistic organisms. Many NTM are of low pathogenicity, and some form of host impairment is necessary to enhance clinical disease. The MTC causes tuberculosis (TB) and *M. leprae* causes leprosy, whereas NTM can cause mycobacteriosis [1–4].

The MTC includes *M. tuberculosis*, *M. bovis*, *M. bovis BCG*, *M. africanum*, *M. caprae*, *M. microti*, *M. pinnipedii*, *M. canettii*, and *M. mungi*. The species of this complex are obligate pathogenic mycobacteria; they cannot survive in the environment for long periods and therefore can cause infection in humans and/or animals. *M. tuberculosis*, the most prominent member of the MTC, is an obligate human pathogen and the causative agent of TB, which remains one of the leading global public health problems [1–3].

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Runyon, in 1959, was the first to propose a classification for NTM, based on rate of growth in vitro and in pigment production, dependent or not on exposure to light. Two classifications were developed according to these criteria: (1) slow-growing mycobacteria (groups I–III), which require 2–3 weeks of incubation; and (2) rapid growers (group IV), which have the ability to grow in 3–5 days. The slow growers include three groups: group I, the mycobacteria photo-chromogens, which produce pigment after exposure to light; group II, the mycobacteria scotochromogens, which produce pigment in both the presence and absence of light; and group III, the mycobacteria nonchromogens, which are unable to produce pigment [13] (Table 7.1).

Owing to the complexity of the Runyon classification and its infrequent use in medical practice, the Kazda classification of mycobacteria is more widely used. Kazda used the pathogenicity of mycobacteria in humans and cataloged them into three groups: obligate pathogenic mycobacteria, potentially pathogenic mycobacteria, and rarely pathogenic mycobacteria. The obligate pathogenic mycobacteria include MTC and *M. leprae*. Those classified as potentially pathogenic and rarely pathogenic mycobacteria are termed NTM [1, 2] (Table 7.2).

Table 7.1 Nontuberculous mycobacteria that cause cutaneous diseases [1]

Group	Pigment production	Rate of growth	Main pathogens
I	Photochromogens	2–3 weeks	*M. kansasii, M. marinum, M. simiae*
II	Scotochromogens	2–3 weeks	*M. scrofulaceum, M. gordonae, M. szulgai, M. xenopi*
III	Nonchromogens	2–3 weeks	*M. avium, M. intracellulare, M. ulcerans, M. haemophilum, M. nonchromogenicum M. genavense, M. terrae, M. malmoense*
IV	Pigmented or unpigmented	3–5 days	*M. fortuitum, M. abscessus* subsp. *abscessus, M. abscessus* subsp. *bolletii, M. abscessus* subsp. *massiliense, M. chelonae, M. smegmatis, M. immunogenum, M. goodii, M. wolinskyi, M. cosmeticum, M. mucogenicum*

Table 7.2 Pathogenic species of mycobacteria [1, 2]

Obligate pathogenic mycobacteria				
M. leprae	*M. tuberculosis*	*M. bovis*	*M. caprae*	*M. africanum*
M. microti	*M. pinnipedi*	*M. canettii*	*M. mungi*	
Potentially pathogenic mycobacteria				
M. avium subsp. *avium*	*M. avium* subsp. *paratuberculosis*	*M. avium* subsp. *hominissuis*	*M. avium* subsp. *silvaticum*	*M. intracellulare*
M. fortuitum	*M. abscessus* subsp. *abscessus*	*M. abscessus* subsp. *bolletti*	*M. abscessus* subsp. *Massiliense*	*M. chelonae*
M. marinum	*M. kansasii*	*M. szulgai*	*M. scrofulaceum*	*M. xenopi*
M. peregrinum	*M. asiaticum*	*M. branderi*	*M. simiae*	*M. genavense*
M. ulcerans	*M. haemophilum*	*M. celatum*	*M. immunogenum*	*M. lentiflavum*
M. malmoense				
Rarely pathogenic mycobacteria				
M. agri	*M. cookii*	*M. phlei*	*M. alchiense*	*M. farcinogenes*
M. gordonae	*M. terrae*	*M. diernhoferi*	*M. hassiacum*	*M. porcinum*
M. pulveris	*M. tokaiense*	*M. obuense*	*M. thermoresistibile*	*M. duvalii*
M. homossenze	*M. alvei*	*M. aurum*	*M. confluentis*	*M. gastri*
M. brumae	*M senegalense*	*M. fallax*	*M. lepraemurium*	*M. rhodesiae*
M. triviale	*M. vaccae*	*M. farcinogenes*	*M. mucogenicum*	*M. austroafricanum*
M. chitae	*M. flavescens*	*M. nonchromogenicum*	*M. neoaurum*	*M. obuense*
M. smegmatis	*M. gadium*	*M. shimoidei*	*M. gilvum*	*M. chubuense*
M. sphagni	*M. shottsii*	*M. hiberniae*		

Epidemiology

The genus *Mycobacterium* comprises more than 174 species and 13 subspecies, including MTC and *M. leprae* (obligate pathogenic mycobacteria), and NTM (potentially pathogenic mycobacteria and rarely pathogenic mycobacteria) [1, 4]. NTM are generally considered to be environmental saprophytes widely distributed in nature, and can be found in numerous niches including soil, water, wild and domestic animals, fish, dust, and family and hospital settings. Mycobacteria are widespread in the environment, particularly in aquatic reservoirs. The literature includes reports of infections by *Mycobacterium abscessus* after mesotherapy, acupuncture, tattooing, insulin injections, and surgical procedures, and in patients with diabetes [5–8]. Worldwide, pulmonary disease caused by NTM seems to be increasing. Nevertheless, accurate data to support this assumption are difficult to produce. NTM disease is not a reportable condition in most countries, and is therefore not considered a public health concern. However, the organisms are ubiquitous in the environment, and substantial evidence shows that the environmental niche for *Mycobacterium intracellulare* (the most common pulmonary pathogen) is in biofilms lining suburban water pipes. The *Mycobacterium avium* complex (MAC) includes both *M. avium* and *M. intracellulare* [9–13]. Conversely to *M. tuberculosis*, for which no environmental reservoir exists, NTM are ubiquitous organisms and are readily isolated from environmental sources, including soil as well as both natural and artificial water systems [1, 3, 5, 10]. Many NTM pathogens have been isolated from drinking water. Some clinicians believe that the condition should be classified as an environmental health concern [10]. NTM can be isolated from both natural and man-made environments. Numerous studies have identified various NTM in municipal water systems as well as in hospital water systems and storage tanks. *Mycobacterium fortuitum* is the most common of the rapidly growing mycobacteria (RGM) encountered in clinical practice or in clinical microbiology laboratories [11–13]. *Mycobacterium marinum* is also considered the primary cause of mycobacteriosis in fish in aquariums, aquaculture, and natural settings. *M. marinum* can remain viable in the environment (soil and water) for 2 years. The ability of NTM to form biofilms at fluid–surface interfaces (e.g., interior surfaces of water pipes) contributes to the organisms' resistance to chemical inactivation and provides a microenvironment for growth and proliferation [1, 7, 14–18]. *Mycobacterium ulcerans* is a slow-growing acid-fast bacillus that causes a cutaneous infection known as Buruli ulcer (BU), now considered the third most common mycobacterial infection in immunocompetent humans. BU is prevalent in tropical countries, with prominent foci in West Africa, Central Africa, and the Western Pacific. Cases have also been reported from Asia and the Americas [14]. The true incidence and prevalence of MAC infection worldwide is unknown. The most common nontuberculous species causing human disease in the United States are the slowly growing species of MAC and *Mycobacterium kansasii* and the rapidly growing species *M. abscessus*. Prior to improved combination therapy for human immunodeficiency virus (HIV) infection, between 25% and 50% of acquired immune deficiency syndrome (AIDS) patients in the United States were infected with MAC, and proportions were similar in other parts of the developed world. Since the introduction of potent antiretroviral therapies, these proportions have been reduced considerably in the developed world [11–13].

Etiopathogenesis

NTM are ubiquitous organisms that cause diverse types of infectious disease in human organs, including lung, lymphatic, disseminated, skin, soft tissue, and bone disease. NTM are *Mycobacterium* species that differ from MTC. NTM are widely distributed in the natural environment but may be important pathogens in immune-compromised individuals, such as persons who have HIV or AIDS, patients with congenital and chronic degenerative diseases, and females who have chronic difficulty with expectoration. Progressive lung disease and

extrapulmonary localizations such as skin and soft tissue infections, lymphadenitis, and dissemination are clinically recognized forms, although there is no evidence of animal-to-human and human-to-human transmission. The four most common forms of human diseases associated with NTM are (a) pulmonary disease in adults; (b) cervical lymph node disease in children; (c) skin, soft tissue, and bone infections; and (d) disseminated disease in immunocompromised patients. NTM can colonize patients in healthcare facilities through consumption of contaminated water or ice or through inhalation of aerosols. Colonization following NTM exposure, particularly of the respiratory tract, occurs when a patient's local defense mechanisms are impaired [13, 18–25].

Several reports have suggested that the incidence of nontuberculous mycobacterial lung disease (NTM-LD) has recently been increasing. Although *Mycobacterium* species vary significantly by geographic region, MAC has been reported as the dominant species in NTM-LD. In Japan, *M. avium* is most commonly isolated from the respiratory tract, followed by *M. intracellulare* [9, 24–26]. *M. kansasii* is considered the most virulent of the NTM; it is the second most frequent NTM in patients with AIDS, being surpassed only by MAC [26, 27]. *M. fortuitum* is a rapidly growing NTM, often acquired from environmental sources such as soil and water. It is considered an opportunistic pathogen often associated with trauma, surgical procedures, or immunodeficiency. Skin and soft tissue infection usually is a consequence of direct inoculation. Although several mycobacterial organisms have been associated with skin lesions, only *M. fortuitum/chelonae/abscessus* (Group IV, rapid growers) and *M. marinum* are common pathogens [28, 29]. In the past, human outbreaks of *M. marinum* were sporadic and most commonly associated with contaminated swimming pools. In the last decade there has been a small but steady increase in the frequency of *M. marinum* infections. *M. marinum*

is ubiquitous and is found worldwide in bodies of fresh water, brackish water, and salt water. In humans, breaks in the skin serve as an entry point for the organism during contact with contaminated water sources or infected fish [1, 7, 18]. The infections caused by NTM are clinically indistinguishable from those caused by *M. tuberculosis*, although the therapeutic regimen differs between the MTC and NTM, even among different species of NTM [24–26, 30].

Clinical Presentation

NTM occur in the presence or absence of immunosuppression, although they are more frequent in the former situation. The immune status of the host, the type of mycobacteria, and the entry points influence the clinical presentation. The infection is usually localized in immunocompetent individuals with one or multiple entry points, such as via tattooing, mesotherapy, or acupuncture, while it is usually widespread in immunocompromised individuals.

In broad terms, NTM can cause four clinical syndromes in humans:

I. Pulmonary disease. Particularly in older persons, caused by MAC and *M. kansasii*. Lung disease can be caused by other species: *M. abscessus*, *M. fortuitum*, *M. xenopi*, *M. malmoense*, *M. szulgai*, and *M. simiae.*

II. Superficial lymphadenitis. In children, caused mostly by MAC, *M. scrofulaceum*, and, in northern Europe, *M. malmoense* and *M. haemophilum.*

III. Disseminated disease. In immunocompromised patients it is mostly caused by MAC, but also by *M. abscessus*, *M. fortuitum*, and *M. chelonae* (RGM).

IV. Skin disease and soft tissue infection (SSTI). Frequently as a consequence of direct inoculation by *M. marinum* and *M. ulcerans* (BU). Surgical site infection can be caused by RGM species [31–34].

Nontuberculous Mycobacteria of Dermatologic Interest

Mycobacterium marinum

M. marinum is the most common atypical mycobacteria (NTM) that causes opportunistic infection in humans. After an average incubation period of 2–3 weeks, the initial lesion develops. This is either a solitary nodule or pustule that may break down to form an ulcer or abscess, which can become a verrucous plaque. This lesion develops the initial injury site. *M. marinum* can cause superficial infections and localized invasive infections in humans. It can cause skin lesions which are single, papulonodular lesions, confined to an extremity, or may resemble cutaneous sporotrichosis. Deeper infection can occur as a result of direct extension of cutaneous infection and can lead to tenosynovitis, bursitis, arthritis, and osteomyelitis. Disseminated infections and visceral involvements have been reported in immunocompromised patients [35]. Lesions are most common on the elbows, knees, and feet of swimmers, and dominant hand and fingers of fish fanciers. However, nowadays, because of chlorination disinfection of pool water, *M. marinum* infection rarely occurs [36].

Mycobacterium fortuitum, M. abscessus, M. chelonae, M. smegmatis (RGM)

These species of RGM are capable of producing various diseases in humans ranging from cutaneous infection to disseminated infection; hematogenously disseminated infection is usually seen only in immunocompromised hosts [37]. The majority of infections are due to accidental inoculation from trauma, surgery, injection, or cannulation. The clinical presentation can be nonspecific, so a high index of suspicion is necessary for diagnosis. Cutaneous disease seems to follow patterns. In immunocompetent individuals an abscess is formed at the location of traumatic injury. In immunocompromised hosts (due to organ transplantation, rheumatoid arthritis, renal failure, or autoimmune disorders), patients present with disseminated dis-ease with multiple subcutaneous nodular lesions, cervical lymphadenitis, keratitis, and endocarditis (Figs. 7.1, 7.2, and 7.3). *M. chelonae* is strongly associated with concomitant corticosteroid therapy [34, 38].
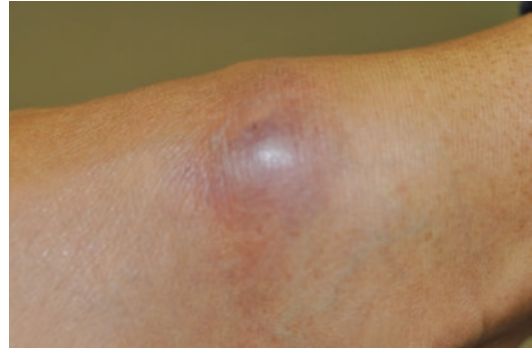
Fig. 7.1   *M. abscessus* in renal transplant

Fig. 7.2   *M. abscessus* in renal transplant

Fig. 7.3   *M. abscessus* in renal transplant

The ***M. fortuitum* group** is responsible for 60% of community-acquired localized cutaneous infection cause by RGM, but is a rare cause of pulmonary disease. It accounts for the majority of nosocomial cases. Most cases present with a single lesion, usually a single subcutaneous nodule located at a site of traumatic injury, surgery, tattooing, mesotherapy, or acupuncture (Figs. 7.4 and 7.5). Disseminated disease has been documented in immunocompromised patients, particularly HIV/AIDS patients. In this population, infection due to *M. fortuitum* can present with lymphadenopathy in the absence of skin lesions [39, 40].

Fig. 7.5 *M. fortuitum* after mesotherapy

The ***M. chelonae/abscessus* group** is responsible for 95% of disseminated cutaneous infections caused by RGM and can also cause chronic lung disease.

M. chelonae

The classic cutaneous presentation is disseminated disease with multiple lesions in the form of tender, erythematous, draining nodules. Lesions are the most commonly seen on the distal parts of the limbs or in a sporotrichoid pattern. Some patients present with a chronic, nonhealing cellulitis or skin ulcers, usually painful and slowly spreading [41]. They are not normally accompanied by poor general condition or involvement of internal organs [42].

M. abscessus **Group**

Although known about 40 years ago, it was only in 1992 that *M. abscessus* was separated from *M. chelonae* and recognized as pathogen responsible for a wide spectrum of soft tissue infections (after trauma or surgery), pulmonary infections, and disseminated disease in immunocompromised patients. There are reports of infections by *M. abscessus* after mesotherapy, acupuncture, tattooing, insulin injections in diabetic patients, and other surgical procedures [8, 43, 44]. In immunocompetent individuals the initial presentation includes the formation of a tender, fluctuant, subcutaneous abscess at the inoculation site. Other presentations include ulcerations, draining sinuses, or nodules. The

Fig. 7.4 *M. fortuitum* in locale of traumatic injury

primary lesion is often followed by a sporotrichoid appearance of ascending lymphadenitis. In immunocompromised hosts, *M. abscessus* can cause disseminated disease. Patients present with systemic symptoms and often have multiple, red to violaceous subcutaneous nodules, and lymphadenopathy. *M. massiliense* (a subspecies of the *M. abscessus* complex) was identified as causative agent of surgical site infection after cesarean section [45]. Infection that involves the *M. smegmatis* group has included cellulitis, localized abscesses, and osteomyelitis after trauma.

Mycobacterium ulcerans

The main virulence factor of *M. ulcerans* is mycolactone toxin that causes extensive necrosis and local immunosuppression [46]. The disease can progress with minimal pain or fever. Infection with this agent leads to extensive destruction of the tissues with the formation of large ulcers particularly on exposed parts of the body, such as the limbs, head, and neck (BU) [47]. The disease typically begins as a painless small nodule (less than 5 cm in diameter). Other possible clinical presentations include papules, plaques, and subcutaneous edema. While the extremities are most often involved, other less affected areas are the head, neck, trunk, and genital area (Fig. 7.6). After a few days to weeks, the initial ulcer lesion develops indeterminate edges, progressing slowly and painlessly (pain may mean secondary infection). Osteomyelitis can occur in 15% of cases [48]. Healing of *M. ulcerans* lesions may occur spontaneously by secondary intention after sloughing of the epidermis and subcutaneous fat with later re-epithelialization. Scarring often leads to contractures, subluxation of joints, disuse atrophy, and distal lymphedema. Over many years, these scars may develop into squamous cell carcinoma (Marjolin's ulcer). Patients with HIV are not at increased risk of infection with *M. ulcerans* [49].

Mycobacterium avium-intracellulare Complex

MAC remains the most frequent bacterial opportunistic infection in persons with AIDS and typi-

Fig. 7.6 Ulcer with undermined edges resembling leishmaniasis in atypical mycobacteriosis due to *Mycobacterium ulcerans* (Buruli ulcer) (Courtesy, Francisco Almeida, MD)

cally causes disseminated disease in the setting of advanced immunosuppression [50]. In these patients, immune reconstitution inflammatory syndrome (IRIS), a frequent complication of MAC disease, most commonly presents with fever and lymphadenitis after the CD4 count increases in response to antiretroviral therapy (ART) [51].

In patients with AIDS who are not on ART, MAC disease typically is a disseminated, multi-organ infection. Early symptoms may be minimal and can precede detectable mycobacteremia by several weeks. Symptoms include fever, night sweats, weight loss, fatigue, diarrhea, and abdominal pain. Nowadays, disseminated MAC is becoming more common

in patients receiving immunosuppressive medications [52]. Localized manifestations of MAC disease have been reported most often in patients who are receiving and have responded to ART, and may also be manifestations of IRIS [51, 52].

In immunocompetent hosts, infection usually occurs in patients with predisposing lung conditions (silicosis, cystic fibrosis). Chronic pulmonary infection is the most common form of human disease (similar to tuberculosis). Osteomyelitis and granulomatous tenosynovitis have both been reported, and MAC is an important cause of cervical lymphadenitis in children. Involvement of the skin is uncommon, but can occur following traumatic skin inoculation in cervical lymphadenitis. Skin lesions are of variable appearance and include multiple ulcers, nodules, ulcerated nodules, abscesses, painless nodules, and plaques [53].

Mycobacterium kansasii

This bacterium typically causes pulmonary disease resembling tuberculosis. It may also cause superficial cervical lymphadenopathy in young children, meningitis, tendonitis, synovitis, tenosynovitis, arthritis, osteomyelitis, or carpal tunnel syndrome [54]. Primary skin lesions have been reported in patients exposed to contaminated water, particularly after local trauma. Disseminated disease can occur in immunocompromised patients (*M. kansasii* is the second most frequent cause of disseminated mycobacteriosis in AIDS patients after MAC), but in immunocompetent patients typically the disease is localized, indolent, and confined to skin. The lesions may be present in sporotricoid distribution, as well as ulcers that do not heal, verrucous papules, papulopustules with necrotic centers, erythematous plaques, nodules, and cellulite [55].

Mycobacterium scrofulaceum

The name *M. scrofulaceum* derives from "scrofula," an infection of the cervical lymph nodes.

Generally it affects children. Local infections resulting from contamination during surgical procedures involving lymph nodes may occur. Submandibular and submaxillary nodes are usually involved, and the disease is often unilateral with few constitutional symptoms, and can resolve spontaneously [56]. Recently, however, isolating *M. scrofulaceum* in childhood lymphadenitis has become increasingly rare, while the incidence of other nontuberculous, environmental mycobacteria, especially *M. avium* and several newly identified species, has increased [57, 58]. Skin abscesses have been reported, as well as chronic ulcerative and nodular skin lesions and pulmonary infection in a patient with AIDS. However, intrathoracic disease and, more rarely, disseminated disease are reported in children [59].

Mycobacterium szulgai

M. szulgai is an uncommon mycobacterial pathogen of humans that causes pulmonary disease resembling the common type of *M. tuberculosis* infection, as well as extrapulmonary infections. It causes mainly pulmonary infection but can also affect osteoarticular system structures (bones, tendons, and bursa), lymph nodes, and skin. Skin lesions can be of various inflammatory patterns, nodules, and cellulite [60]. *M. szulgai* was reported in one case after a previous appendectomy in an immunocompetent patient with a mixed SSTI [61].

Mycobacterium haemophilum

M. haemophilum has emerged as an important human pathogen, causing mainly opportunistic infections in severely immunocompromised patients. It mainly affects AIDS patients (most cases) and organ transplant recipients. Immunocompromised adults may present different types of skin lesions such as plaques, nodules, and bluish-red pustules, unique and painful, which progress to abscess and ulceration. Lesions, which may be multiple, are found most commonly on the extremities, often over joints. The bacilli can cause contiguous septic arthritis,

osteomyelitis, and pneumonia. Healthy children, when infected, usually have cervical lymphadenitis, submandibular and perihilar [62]. Although cervical lymphadenitis has only been described so far in immunocompetent adults and children, one case in an immunocompromised adult was reported [63].

Other Species of Mycobacteria

The clinical importance of *M. malmoense*, *M. genavense*, and *M. xenopi* has been increasingly recognized throughout the world. They rarely cause disease in humans but are increasingly clinically significant. *M. xenopi* is usually considered a commensal, saprophyte, or environmental contaminant. Its pathogenicity is relatively low, and infection requires impairment of host immunity. Infection usually occurs in the lungs in patients with chronic obstructive pulmonary disease, chronic alcoholism, diabetes mellitus, and malignancies [64]. *M. malmoense* is the second most frequently isolated NTM in northern Europe but is rare in the far north. The most common site of

infection caused by this organism is the pulmonary system, particularly in patients with chronic lung disease. However, extrapulmonary infection within lymph nodes, joints, and tendon sheaths has been reported. Of the few cases of disseminated infection with *M. malmoense* that have been published, most were in patients with an underlying immunodeficiency. Primary cutaneous infections are rare, although skin involvement due to a widespread infection may occur [65]. *M. genavense* is recognized as a life-threatening pathogen in severely immunocompromised patients, mostly in those with AIDS. The majority of reported cases are disseminated. These patients present with symptoms similar to those of disseminated MAC infection and can include fever, abdominal pain, diarrhea, weight loss, lymphadenitis, hepatosplenomegaly, and progressive anemia, the bowel being the most affected organ. In healthy patients the symptoms can be nonspecific [66]. Other less commonly reported localizations are cutaneous, cerebral as a solitary lesion, and genital tract [67] (Table 7.3).

Table 7.3 Frequent agents according to population and clinical manifestation

Syndromes	Most affected population	Main agents involved
Pulmonary	Older person	MAC, *M. kansasii*, *M. abscessus*, *M. fortuitum*, *M. xenopi*, *M. malmoense*, *M. szulgai*, *M. simiae*
	Immunocompromised	
	Predisposing lung conditions – chronic obstructive pulmonary disease, bronchiectasis, pulmonary fibrosis, silicosis, cystic fibrosis, pulmonary tuberculosis sequelae	
Lymphadenitis	Children	MAC, *M. scrofulaceum*, *M. malmoense*, *M. Haemophilum*, *M. kansasii*
	Immunocompromised HIV/AIDS	
Disseminated disease	Several immunocompromised/AIDS	MAC, *M. kansasii*, *M. abscessus*, *M. fortuitum*, *M. chelonae*, *M. genavense*
Skin and soft tissue infections (SSTI)	Exposure to water/fish environments (*M. marinum* = fish-tank granuloma)	*M. marinum*, *M. ulcerans* (Buruli ulcer)
	Trauma	*M. abscessus*
	Surgical procedures	
	Surgical site infection	
Osteoarticular disease	Trauma	*M. fortuitum*, *M. abscessus*, *M. chelonae*, *M. marinum*, *M. ulcerans*, *M. szulgai*
	Continuous seeding	

Complementary Examinations

The diagnosis of NTM disease requires caution because the isolation from non-sterile clinical specimens can lead to contamination or transient colonization. Therefore, the clinical-laboratory correlation is extremely important for establishing the diagnosis of disease by NTM and for determining the therapeutic strategy. Biopsies should be collected aseptically and placed in sterile vials containing sterile distilled water or sterile saline solution of 0.9% (never formaldehyde). Transport to the laboratory should occur immediately, at room temperature. Shaved skin or dry superficial lesions have little value in diagnostic mycobacteriosis. Diagnosis can be given through the histopathology, smear, culture, and phenotypic identification, and by molecular biology for species detection and identification. Microscopic features are considered (morphology of the bacillus, cord factor detection) and macroscopic culture (pigmentation and morphology) [68] (Table 7.4).

Table 7.4 Complementary examinations for NTM

Microbiological diagnosis
(A) Investigation of acid-fast bacilli in stained smear
(B) Mycobacterial culture
(C) Phenotypic identification of the species
(a) Production of carotenoid pigments
(b) Growth time in culture
(c) Antimicrobial susceptibility testing (AST)
Molecular diagnosis
(A) Polymerase chain reaction (PCR)
Conventional or in-house PCR
Nested PCR
Real-time PCR
Multiplex PCR
PCR with hybridization
PCR in situ
(B) Identification of mycobacterial species (genotyping)
(a) DNA (genetics) probes
(b) Gene sequencing
Mycobacteria mobility shift assay (MMSA method) – (16S rRNA gene)
Polymorphism restriction analysis of hsp65 gene (PRA hsp65 method)
Histopathologic diagnosis

Microbiological Diagnosis

Investigation of Acid-Fast Bacilli in Stained Smear

The *smear is the direct* AFB, usually by Ziehl–Neelsen staining or one of its modifications, such as the Kinyoun stain, and is examined by routine light microscopy. All mycobacteria share the characteristic of acid-fastness. Its disadvantage is limited sensitivity, requiring 5000–10,000 bacilli per milliliter of sample to obtain a positive result, and moreover requires a skilled and experience microscopist [34, 68].

Mycobacterial Culture

The *culture* is the most sensitive method available for the bacteriological diagnosis of mycobacterial infections, detecting from 10 bacilli/ml in the sample. From the culture, it is also possible to identify the mycobacteria isolated and the completion of antimicrobial susceptibility testing (AST). For most of the mycobacteria, the optimum growth temperature ranges from 35 to 37 °C, except the ones that grow *M. ulcerans* (28–33 °C), *M. marinum* (31 °C), and *M. haemophilum* (30–32 °C). For growth, solid media, such as Lowenstein–Jensen (LJ) and Middlebrook 7H10 and 7H11, and liquid media, such as Kirchner or Middlebrook 7H9 broth, can be used. The *M. haemophilum* has the unique characteristic that differentiates it from all other species of the genus: it requires hemin or ferric ammonium citrate to grow in culture media [69]. The readings should be taken 48 h after seeding and incubation (to check if there is contamination) and, subsequently, every 7 days to 8 weeks to complete. As the time of bacterial growth varies from 2 to 6 weeks, culture has the disadvantage of the prolonged time required for the release of results. Therefore, semi-automatic and automated systems have been developed to reduce the time to results to 1–4 weeks. These systems utilize radiometric and/or colorimetric assays for the detection of CO_2 produced and O_2 consumed during bacterial growth. Cases of NTM infection are considered to present a sample with positive cultures from a sterile site or two or more samples with positive culture, with more than 10 colonies, from a non-sterile site [70].

Phenotypic Identification of the Species

The earliest discriminatory methods relied upon phenotypic characteristics, such as colony morphology, susceptibility to antituberculosis drugs, or mycobacterial phage typing. The usefulness of these methods is seriously limited by the phenotypic variability of mycobacteria. The biochemical and serological characteristics of NTM produced no success [3, 26, 71].

According to the phenotypic characteristics, the NTM can be classified based on the:

(a) *Production of carotenoid pigments*
  According to these criteria, mycobacteria *slow growers* (Groups I, II, and III) require 2–3 weeks of incubation and mycobacteria *rapid growers* (Group IV) have the ability to grow in 3–5 days.
(b) *Growth time* in culture
  This *method* depends on the rate of growth in vitro and in pigment production, dependent or not on exposure to light (Runyon 1959) [1–3]. RGM are considered those which develop visible colonies on solid media in less than 7 days (*M. fortuitum*, *M. chelonae*, *M. abscessus*) and slow growth (*M. marinum*, *M. kansasii*, *M. scrofulaceum*, MAC, *M. ulcerans*) those which develop visible colonies on solid media over 7 days. These time-consuming methods are being replaced with more rapid techniques, including molecular methods.
(c) *Antimicrobial susceptibility testing*
  AST for NTM may be performed to determine which antimicrobial drugs will be most effective in treating the infection [26]. The main limitations of the phenotypic method consist in the delay in obtaining results, the differentiation of difficulty of various species, and dubious results that can be displayed by some biochemical tests, besides being laborious. There are many methods that can be applied to the determination of the isolated species. Routinely strains identified as NTM are not applied, because there are few studies on the correlation of the results of in vitro AST and

clinical prognosis. The gold-standard method for AST of NTM is broth microdilution. The technique used is the MIC (minimum inhibitory concentration in liquid medium) and is only performed for some species: MAC, *M. kansasii*, *M. chelonae*, *M. abscessus*, and *M. fortuitum*. The MIC is expressed in μg/ml and is typically indexed to base 1 (e.g., 1, 2, 4, 8, 16, and 32 μg/ml). Routine AST of MAC isolates is recommended for clarithromycin only, which can be detected by a mutation in the 23S ribosomal macrolide binding, while *M. kansasii* isolate is recommended for rifampicin only. Both taxonomic identification and treatment of RGM should be with amikacin (*M. fortuitum*, *M abscessus*, and *M. chelonae*), imipenem (*M. fortuitum* only), doxycycline, the fluorinated quinolones, a sulfonamide or trimethoprim-sulfamethoxazole, cefoxitin, clarithromycin, linezolid, and tobramycin (*M. chelonae* only) [3, 26, 71].

Molecular Diagnosis

Owing to the recent increase in the isolation of new species and the availability of modern methods for species identification, conventional methods have become inadequate. Molecular identification has greatly aided the diagnosis of mycobacteriosis to its present speed and accuracy. However, the interpretation of results should always take into account the clinical data of the patient. Among the techniques used for diagnosis are those that promote the amplification of genetic material, such as the *polymerase chain reaction* (*PCR*) and its variations (e.g., conventional or in-house PCR, nested PCR, real-time PCR, and multiplex PCR). In addition, for the identification of mycobacterial species (*genotyping*) there are techniques that employ *DNA* (*genetic*) *probes* and *Gene* (*DNA*) *sequencing* from the PCR products, such as mycobacteria mobility shift assay (*MMSA method*) and polymorphism restriction analysis of hsp65 gene (*PRA hsp65 method*). These techniques include *specific nucleic acid probes*.

Polymerase Chain Reaction

The PCR technique is based on the enzymatic amplification of a specific DNA sequence. This reaction occurs in cycles, which consist of three steps: denaturation, pairing, and extension. In the case of mycobacteria, the amplified DNA sequence can be common to all bacteria of the genus or be specific to a species or complex. An example of the latter is the insertion of IS6110, most commonly used for sequence-specific amplification DNA of MTC. Most protocols use the IS6110 insertion repetitive sequence of 1350 base pairs present in the MTC species with different numbers of copies integrated into various chromosomal sites. By being present in multiple copies in the genome, this molecular target technique provides an increase in sensitivity, which represents an advantage over other targets. However, the disadvantage lies in the existence of *M. tuberculosis* isolates that have lost the IS6110 sequence, which has been observed mainly in Asia. When the amplified sequence is common to the genus, the diagnosis is *Mycobacterium* sp. In this case, the region of 16S ribosomal DNA (rDNA) is a key target identification to be highly conserved and includes differences in the specific nucleotide sequence of a group or species. For this reason, the amplified product can also be used for further molecular species identification of mycobacteria. PCR amplifies a 1027 bp highly conserved region of the 16S rRNA gene that is present in all mycobacteria. This method presents results comparable with those of the other molecular methods of identification with the advantage of being fast, identifying mycobacteria within 6 h of the culture. *M. ulcerans* has multiple copies of IS2404 (>200) in its genome, which is not observed in any other mycobacteria [72].

Identification of Mycobacterial Species (Genotyping)

(a) *DNA* (*genetics*) *probes*, such as the AccuProbe System (Gen-Probe, USA), INNO-LiPA Mycobacteria Assay (Innogenetics, Belgium), and the GenoType *Mycobacterium* Assay (Hain Lifescience, Germany), are methods of rapid species identification, and have been available for some time for identification of clinically important mycobacterial species, including MTC, MAC, *M. kansasii*, and *M. gordonae*. The tests are based on species-specific DNA probes that hybridize with rRNA released from bacteria. However, probes are not available for all pathogenic mycobacterial species, and those isolates must be identified by other methods. In addition, the MTC probe cannot differentiate between the members of this complex (*M. tuberculosis*, *M. bovis*, *M. bovis* BCG, *M. africanum*, and *M. microti*) [26, 73].

(b) *Gene sequencing* (PCR-based sequencing) has become the gold standard for identification of mycobacterial species. The method consists of PCR amplification of mycobacterial DNA with genus-specific primers and sequencing of the amplicons. The automation of sequence analysis is enabled by the introduction of commercial systems like the MicroSeq 500 16S rDNA Bacterial Sequencing Kit (PE Applied Biosystems, USA), in which a 500-bp sequence of the NTM is analyzed and compared with a commercially prepared database. The target most commonly used is the gene coding for the 16S ribosomal RNA. Mycobacterial species identification by the *MMSA* is based on microheterogeneities in nucleotide sequences of the 16S rRNA gene with PCR amplification of a 1027 bp highly conserved region of the 16S rRNA gene that is present in all mycobacteria. The MMSA method was designed for NTM and MTC species identification using PCR products from mycobacterial DNA coding for the 16S rRNA gene derived from culture to show specific heteroduplexes formed among different *Mycobacterium* species [26, 30, 73].

Several other target genes have been characterized for this purpose. In 1993 Telenti and colleagues described PCR followed by restriction endonuclease assay analysis, the *Polymorphism Restriction Analysis* (*PRA*) *of hsp65 gene* (*PRA hsp65 method*), which differentiates most NTM species, but not the MTC. This method is based on the amplification, by PCR, of a sequence fragment of 441 bp of the *heat shock protein*

gene of 65 kDa (hsp65) containing specific epitopes shared by various species of mycobacteria. The PRA method is relatively rapid, does not require viable organisms, and identifies many NTM species that are not identifiable by phenotypic or chemotaxonomic techniques alone. This method presents as main advantages its high specificity, the release of results in a few hours, and the fact that it requires only basic PCR and agarose gel electrophoresis equipment. However, sometimes species with PRA profiles not yet described in the literature are observed, while others have a shared profile for more than one species, or the same species may even present more of a restriction profile, facts that constitute limitations.[30, 73, 74].

Histopathologic Diagnosis

The most common causes of nontuberculous mycobacteria in SSTI are RGM species (*M. fortuitum*, *M. abscessus*, and *M. chelonae*), *M. marinum*, and *M. ulcerans.* The infiltrate tends to be deeper in immunosuppressed patients, involving the subcutaneous tissue (100%) with a more diffuse distribution and constant abscess

formation (Fig. 7.7). It can include dermal granulomas (occasionally with suppuration), stellate abscesses, sinus tracts, and acute and chronic inflammation [75–77]. AFB are seen in a minority of cases (±20%) [78]. These features are not pathognomonic. The predominant histopathologic findings may vary depending upon the host's immune status. In a review of biopsy specimens from 27 patients with NTM SSTI, granulomas were more common in specimens from immune-competent patients (18 specimens), whereas deep infiltrates into the subcutaneous tissue, abscess formation, and a foamy appearance of macrophages were more common in specimens from immune-compromised hosts (10 specimens from 9 patients). A marked granulomatous inflammatory reaction was observed in 83% of immunocompetent and in 60% of immunosuppressed patients [75]. Histopathologically, the most common findings were diffuse infiltration of mixed inflammatory cells and small vessel proliferation in the dermis (100%). Epidermal proliferation (71%) and dermal granuloma (71%) were also very common. Suppurative granuloma was found in 43% of the cases, and eosinophil infiltration was uncommon (14%), as was eosinophilic infiltra-
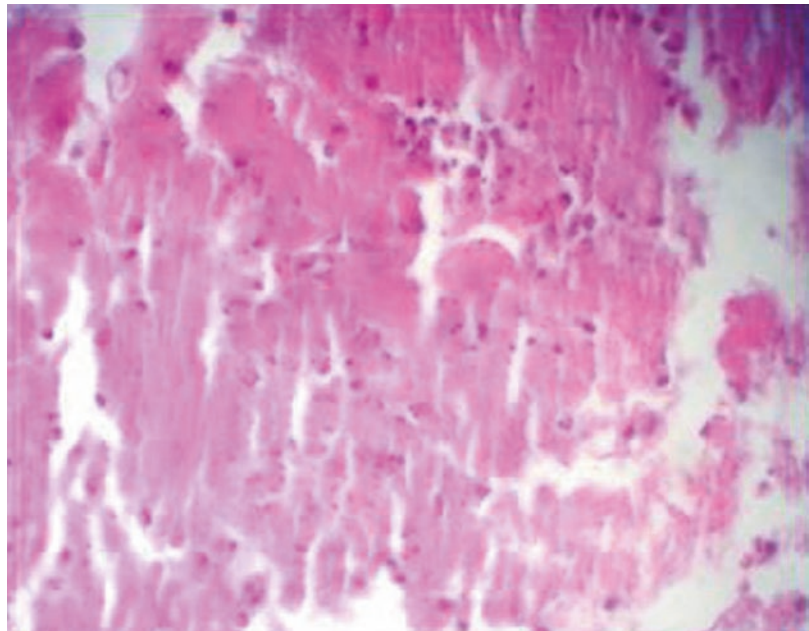
Fig. 7.7 Infectious complications in tattooing (*M. fortuitum*)

tion. The lesions disappear after a mean of 7 months (range, 1.5–12 months) with treatment by oral clarithromycin alone or in combination with other antimycobacterial agents. These clinical and histopathologic data should assist clinicians in the diagnosis of NTM. In patients with negative cultures and PCR, histopathology of tissue specimens demonstrating AFB or granulomas supports the diagnosis. However, the absence of these findings does not exclude NTM disease [75–77].

Differential Diagnosis

M. marinum differential diagnosis should include sporotrichosis, nocardiosis, and leishmaniasis. The tenossinovite can mimic rheumatoid arthritis. On the one hand, infection by *M. fortuitum*, in general, is characterized by the appearance of solitary abscess, but similar nodules in sporotrichosis, folliculitis, and cellulitis have also been described. On the other hand, *M. chelonae* or *M. abscessus* infection is characterized by the production of multiple cutaneous abscesses that can fistulize [78]. The differential diagnosis of BU should include leishmaniasis, basal cell carcinoma, squamous cell carcinoma, gangrenous pyoderma, Kaposi's sarcoma, cutaneous tuberculosis, leprosy, syphilis, tropical ulcers, necrotizing fasciitis, anthrax, noninfectious granulomatous disease, ischemic ulcers, diabetic ulcers, necrobiosis lipoidica, cutaneous lymphoma, and polyarteritis nodosa, among others [79]. The differential diagnosis of MAC should include pyoderma, folliculitis, other causes of panniculitis and ulcers, infective dimorphic fungus, lepromatous leprosy, and tuberculous skin. *M. scrofulaceum* infection should be distinguished from other causes of cervical lymphadenopathy, particularly of *M. tuberculosis* (scrofuloderma). However, *M. tuberculosis* usually affects the (previous) tonsils and cervical lymph nodes, while *M. scrofulaceum* typically affects the submandibular and submaxillary lymph nodes. Where conditions are sporotrichoid by default, there are differential diagnoses with other atypical mycobacteriosis [26, 76–79] (Table 7.5).

Table 7.5 Differential diagnosis of mycobacteriosis

M. marinum	Sporotrichosis, nocardiosis, leishmaniasis; tenossinovite can mimic rheumatoid arthritis
M. fortuitum, *M. abscessus*, *M. chelonae*	Nodules of sporotrichosis, folliculitis, cellulitis, solitary or multiple cutaneous abscesses
M. ulcerans (Buruli ulcer)	Leishmaniasis, basal cell carcinoma, squamous cell carcinoma, gangrenous pyoderma, Kaposi's sarcoma, cutaneous tuberculosis, leprosy, syphilis, tropical ulcers, necrotizing fasciitis, anthrax, noninfectious granulomatous disease, ischemic ulcers, diabetic ulcers, necrobiosis lipoidica, cutaneous lymphoma, polyarteritis nodosa, among others
M. avium-intracellulare complex (MAC)	Pyoderma, folliculitis, panniculitis, infection dimorphic fungus, tuberculosis, tuberculous skin, lepromatous leprosy, cryptococcal disease, aspergillosis, histoplasmosis
M. scrofulaceum	Other causes of cervical lymphadenopathy, scrofuloderma, sporotricoid conditions

Therapeutic Approach

Mycobacterium marinum

Because of a lack of clinical evidence, treatment must be individualized. Isolates of *M. marinum* are susceptible to clarithromycin, as well as sulfonamides, tetracyclines, rifampicin, and ethambutol. It is necessary to administer combination therapy with two or more drugs for significant cutaneous infections or disseminated disease. For severe infections, a combination of rifampicin and ethambutol seems to be the recommended regime. Monotherapy with clarithromycin, minocycline, doxycycline, ciprofloxacin, and trimethoprim-sulfamethoxazole is typically used for patients with localized, mild, and uncomplicated cutaneous disease. Ciprofloxacin is not recommended because some strains are resistant and monotherapy and carry the risk of mutational resistance. Recent studies have documented unexplained antibiotic resistance to several drugs, including rifampicin and doxycycline. Clarithromycin is currently regarded as the single best agent for first-line monotherapy, although equal success

has been achieved using minocycline and amikacin. The typical duration of therapy is 3–6 months for localized infection and 12 or more months for disseminated disease. Surgical treatment may be required if deep structures are involved. Cryotherapy is also frequently used as a first treatment, although there are effective therapeutic alternatives.

Mycobacterium fortuitum, Mycobacterium chelonae, and Mycobacterium abscessus (RGM)

The treatment generally involves macrolide (clarithromycin 1 g/day or azithromycin 250–500 mg/day) and intravenous agents. Management of these infections requires the use of antibiotic therapy, which is different from that used in the therapy of tuberculosis and other slowly growing NTM. In vitro studies have shown that these species have different susceptibility patterns: *M. abscessus* is usually susceptible to macrolides and cefoxitin, and resistant to quinolones; *M. chelonae* is susceptible to macrolides and resistant to quinolones and cefoxitin; and *M. fortuitum* is susceptible to quinolones and resistant to macrolides. *M. fortuitum* is more sensitive to antibiotics and its recurrence rate is greater than that of *M. abscessus* and *M. chelonae* [79].

Mycobacterium ulcerans

The WHO recommends multidrug therapy for 8 weeks with rifampicin and streptomycin. The recommended doses of rifampicin and streptomycin are: rifampicin, 10 mg/kg, oral, daily; streptomycin, 15 ml/kg, intramuscular, daily. The latter drug is contraindicated in pregnant women. In 2014, a group of BU scholars in Australia, with the approval of the Australasian Society for Infectious Diseases, published guidelines for the treatment of BU, in which they recommended oral rifampicin and clarithromycin or fluoroquinolones (moxifloxacin and ciprofloxacin) [72]. In advanced cases, surgery includes debridement and skin grafting. There are no guidelines thus far for surgery. The consensus among experts is that surgery should be performed after 4 weeks of antibiotic treatment.

Paradoxic reactions are a recently recognized phenomenon, whereby worsening of a BU lesion is seen during or long after antibiotic treatment. This is now known to be an inflammatory reaction against *M. ulcerans*, and pain and pus may be present. Treatment of paradoxical reactions requires prednisolone. In the past, some cases of paradoxical reactions might have been mistakenly diagnosed as recurrence or relapse [72].

Mycobacterium avium-intracellulare Complex

Treatment includes ethambutol and rifampicin and clarithromycin or azithromycin.

Mycobacterium haemophilum

Although the optimal therapy is still unknown, most successful regimens include clarithromycin, ciprofloxacin, rifampicin, and rifabutin, and surgical treatment should be considered in some cases of localized disease. In vitro, doxycycline and sulfonamides have shown variable susceptibility, and all isolates are resistant to ethambutol. For immunocompromised patients with disseminated or pulmonary infection, it is recommended to continue the established treatment until cultures remain negative for a year. However, the trend in immunocompetent patients is for a shorter treatment duration, between 4 and 12 months depending on age and type of disease.

Mycobacterium szulgai

Therapy with combination of antituberculosis medication based on in vitro susceptibilities for 4–6 months should be successful for extrapulmonary disease (Table 7.6):

Table 7.6 Treatment of the main nontuberculous mycobacteria species

Species	Chemotherapy	Dose	Duration
M. marinum	*Uncomplicated cutaneous disease*: clarithromycin or minocycline; or doxycycline; or ciprofloxacin; or trimethoprim-sulfamethoxazole	500 mg 2×/day or 100 mg 2×/day or 100 mg 2×/day or 500 mg 2× day or 160/800 2×/day	3–6 months
	Disseminated: minocycline + amikacin	100 mg 2×/day + 10–15 mg/kg/day	12 months
M. fortuitum *M. chelonae* *M. abscessus*	Clarithromycin or azithromycin + *Parenteral medications*: amikacin or cefoxitin or imipenem	1000 mg/day or 250–500 mg/day + (10–15 mg/kg/day (max 1 g/day, 5×/ week for 2 months and 2× week from the third month) or 200 mg/day or 30 mg/day/day	6 months
M. ulcerans (BU)	*Localized extensive* rifampicin + streptomycin or clarithromycin or *fluoroquinolones*: moxifloxacin or ciprofloxacin)	Surgery 10 mg/kg oral (max. 600 mg/ day) + 15 ml/kg intramuscular (max. 1 g/day,5× week for first two months and 2× week from the third month) or 500–1000 mg/day or 400 g/day or 500 mg 2× day	2–3 months
M. avium-intracellulare complex (MAC)	Rifampicin + clarithromycin or azithromycin + ethambutol	600 mg/day + 1000 mg/day or 500 mg/ day + 15 mg/kg/day	6–12 months
M. haemophilum	Rifampicin + clarithromycin + ciprofloxacin	600 mg/day + 1000 mg/day + 500 mg 2× day	
M. kansasii	Rifampicin + ethambutol + isoniazid	600 mg/day + 15 mg/kg/day + 5–10 mg/kg/day (max. 300 mg/day)	12 or 18 months with negative culture
M. szulgai	Rifampicin + ethambutol + clarithromycin	600 mg/day + 15 mg/kg/day + 1000 mg/day	6 months

Glossary

Buruli ulcer (BU) Is a disease affecting the skin, tissues, and in some cases the bones, caused by the environmental pathogen *Mycobacterium ulcerans*. Its mode of transmission is still elusive and controversial. Infection with this agent leads to extensive destruction of the tissues with the formation of large ulcers particularly on exposed parts of the body, such as the limbs, head, and neck.

Immune reconstitution inflammatory syndrome (IRIS) Is an inflammatory reaction resulting from restored immunity to specific infectious or non-infectious antigens. It is a frequent complication of MAC disease, most commonly presenting with fever and lymphadenitis after the CD4 count increases in response to antiretroviral therapy (ART), in persons with AIDS. Localized manifestations of MAC disease have been reported most often in patients who are receiving and have responded to ART.

***Mycobacterium avium-intracellulare* complex (MAC)** Includes both *M. avium* and *M. intracellulare*, and represent the most frequent bacterial opportunistic infection in persons with HIV/AIDS.

Marjolin's ulcer Consists of the malignant transformation of a chronic ulcerative lesion. Over many years, these scars may develop into squamous cell carcinoma.

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Sexually Transmitted Diseases

8

Walter Belda Jr.

Key Points Summary
- STDs are diseases transmitted from person to person, with more than 30 cataloged, including viruses, bacteria, and parasites.
- Unprotected sex increases the risk for STDs
- STDs represent a major problem in public health, causing chronic diseases, AIDS, pregnancy complications, infertility, cervical cancer, and death.

Introduction

Nowadays, sexually transmitted diseases (STDs, or sexually transmitted infections, STIs) comprise the most common group of infectious diseases reported in most countries. They maintain a high incidence despite some fluctuation. In an attempt to classify STDs, Pereira and Serruya [1], in 1982, and subsequently Belda [2], in 1999, classified them as described in Box 8.1.

Box 8.1 Update classification of STDs

Essentially transmitted through sexual contact	Frequently transmitted through sexual contact	Occasionally transmitted through sexual contact
Syphilis	Donovanosis	Molluscum contagiosum
Gonorrhea	Non-gonococcal urethritis	Pediculosis
Chancroid	Genital herpes simplex	Scabies
Lympho-granuloma venereum	Genital warts (condyloma acuminatum)	Shigellosis
	Genital candidiasis	Amebiasis
	Hepatitis B	Hepatitis C
	HIV	Emergent virus
	Trichomoniasis	

In this chapter the *essential STDs, genital warts*, and *donovanosis* are addressed.

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Syphilis

A chronic infectious disease that is sexually transmitted, and occasionally of transplacental transmission, caused by *Treponema pallidum*, syphilis is characterized by long periods of medical silence and a clinical ability to affect multiple organ systems, producing skin, mucous membranes, cardiovascular, and nervous system lesions.

Epidemiology

It is a universal disease that affects all social classes, with young people being the most affected, especially those between 15 and 24 years of age, because of their more intense sexual activity; groups of lower sociocultural and economic conditions because they have a greater tendency toward promiscuity; and itinerant groups (sailors, tourists, and military troops) [4, 5]. It progresses in waves that fluctuate because of several causes. The reasons for its upsurge are manifold, being of social and medical origins. Today, sexual life begins earlier. In addition, improved living conditions provide a more prolonged period of sexual activity, increasing the number of individuals at risk of infection. Tourism and professional trips favor the appearance of cases whose contacts of infection cannot be tracked.

Etiopathogenesis

T. pallidum is a thin microorganism devoid of cell membrane, with regular spirals numbering no more than 12. It has rotational, bending, contraction, and translational movements. It reproduces longitudinally by binary fission every 32–36 h. It is very heat-labile and difficult to be cultured [1–3], and should be distinguished from saprophytic treponemas of the oral cavity (*Treponema macrodentium* and *Treponema microdentium*) and preputial area (*Treponema calligra* and *Treponema minutum*), and from genital borrelias. Under dark-field microscopy *T. pallidum* has more spirals, is thinner, does not have deformities

along its displacement, and has slower movements in relation to saprophytic treponemas. Its antigenic constitution is complex, with surface antigens and others inside it.

The infection stimulates humoral and cellular responses, with cellular immunity being established only in a late, latent, or asymptomatic stage [6]. Regarding humoral immunity, the treponemal and non-treponemal antibodies that are detected at high levels in the active stages of the disease do little to protect the host. The immobilizins help minimize the spread of disease and facilitate the destruction of treponemas through defensive mechanisms; however, no correlation exists between immunity and antilipid antibodies since their titrations are very high in recent infections, which are more widespread, and therefore resistance to infection is not developed. In contrast, titrations are low in late forms, when immunity to reinfection is high [3, 6].

The infection is transmitted by direct contact with open lesions or intact mucous membranes, transfusion of contaminated blood, and by transplacental transmission in congenital syphilis. Treponema is able to penetrate intact skin and mucous membranes. At the site of inoculation it multiplies rapidly, and reaches the regional lymph nodes through the lymphatic route, where it also multiplies quickly. Its immediate dissemination also occurs through the blood. In the lymphatic/hematogenous route it rapidly invades the whole body, so that even when the symptomatology is local the infection becomes widespread in a few hours [3, 7]. The first manifestation of acquired syphilis is the syphilitic chancre. The incubation period ranges from 2 to 4 weeks. After about 6 weeks, generalized manifestations of syphilis arise, which constitute the so-called secondary period. This period lasts about 2 years, and is characterized by the successive appearance and disappearance of different, somewhat generalized features. Following this period the clinical manifestations fully disappear, and the so-called syphilitic latency begins. The patient can remain in this state indefinitely. In about 30% of cases, and after a period of 10–30 years, the patient can pass through the tertiary stage, characterized by cutaneous/visceral manifestations, particularly of

a nervous and cardiovascular nature. Currently acquired syphilis is classified as recent and late, considering a year of progression as the boundary between these two stages. Recent acquired syphilis includes primary, secondary, and latent recent syphilis. Late syphilis includes the so-called skin tertiary, cardiovascular, nervous, and latent late syphilis [3, 4, 7].

Clinical Presentation

Primary Syphilis

Primary syphilis is characterized by the appearance of a formerly ulcerated, round or oval, granulomatous lesion with a clean and rosy background on the inoculation point, which emanates transparent *Treponema*-rich serosity, with no adjacent inflammatory phenomena and with borders gently descending to the bottom. The lesion is often single (Fig. 8.1) and painless, even when handled, but due to intense inflammatory infiltrate it presents with hard consistency and is cartilaginous upon palpation. In men it most often affects the balanopreputial sulcus, frenulum, and navicular fossa. In women it is mainly suppurative, painless, and unaccompanied by inflammatory phenomena. In general the nodes are hard, painless, and not adhered to superficial or deep planes. Evolutionarily, the hard chancre lesions tend to heal spontaneously, even with no treatment, around the fourth week after appearance, and generally without scarring [3, 7, 8].

Secondary Syphilis

Manifestations of secondary syphilis appear on average 6–8 weeks after the appearance of the hard chancre. Polymorphic lesions at this stage represent tissue reaction to the presence of *Treponema*, transmitted by lymphatic and/or hematogenous routes. The intensity of tissue reactions will occur depending on the immune status of the host, with which the variations of the various common clinical conditions will also appear. The syphilitic roseola (Fig. 8.2) is the first manifestation to appear, characterized by erythematous, lenticular, oval, or circular macules of inaccurate, isolated, or confluent limits, surrounded by mild scaling. Sometimes these macules infiltrate, gradually becoming papular (papular syphilide). These lesions affect mainly the trunk and roots of limbs, and particularly the palmoplantar regions (Fig. 8.3). In the late secondary period there is a tendency to clustering and location of the lesions, with the genital, anal, and axillary regions and submammary folds developing papular lesions that form papular, secreting plates rich in treponemas (flat condyloma). The lesions in the oral cavity (tongue and lips) have a whitish maceration area on an eroded base. Following the skin and mucosal lesions, so-called "patchy alopecia" may occur, particularly in the parietal and temporal regions; there may be widespread micropolyadenopathy, splenomegaly, hepatitis, nephrotic syndrome, iritis, or iridocyclitis [3, 4, 8, 9].

Fig. 8.1 Hard chancre on the penis

Fig. 8.2 Syphilitic roseola

Fig. 8.3 Sole lesion in secondary syphilis

Early Malignant Syphilis

This rare variant of recent syphilis is considered a variant that affects individuals in poor general condition, who are debilitated due to malnutrition or other pathologies. Today it is believed to be an expression of an immune response to *Treponema pallidum* whereby there is tissue destruction and vasculitis obliterans of medium-caliber vessels. Clinically the lesions are more destructive, are papulopustular in the beginning, and later evolve to clearly defined ulcerous-necrotic lesions covered by rupioid crusts (Fig. 8.4). They affect mainly the face and scalp and are followed by fever, headache, arthralgia, and other systemic manifestations [3, 8].

Late Syphilis

Symptoms of late syphilis arise after varying periods of latency, ranging from 10 to 30 years.

1. Skin lesions: usually arise 2–7 years after secondary nodular or nodulo-ulcerated, clustered lesions that form serpiginous patches with polycyclic halo. When they affect mucous membranes, the lesions can produce changes on the tongue (chronic interstitial glossitis),

Fig. 8.4 Early malignant syphilis

palatal perforation, and destruction of the nasal septum [3].

2. Cardiovascular: the impairment generally occurs 10–30 years after the onset of infection. It is most common in men and black individuals. The most common conditions are aortitis, aortic valve insufficiency, aortic aneurysm, and orificial coronary stenosis, which result in angina [3].

3. Nervous: impairment is found on average 30 years after the start of infection. The condition can be asymptomatic or reveal symptoms of acute syphilitic meningitis, spastic Erb's palsy, aphasia, hemiplegia, tabes dorsalis, and paralytic dementia [10].

4. Other systems: there may be impairment of bones, liver, eyes, gastrointestinal tract, and testes.

Box 8.2 lists the principal clinical manifestations of syphilis.

Box 8.2 Clinical manifestations of syphilis

Stage	Manifestations
Primary	Painless genital ulcer of clear background and hard base
	Noninflammatory regional lymphadenopathy
Secondary	Syphilitic roseola, mucous patches, flat condyloma
	Patchy alopecia, generalized micropolyadenopathy, general symptoms
Tertiary	Cutaneous gummas, interstitial glossitis, aortitis, aortic insufficiency, angina, aphasias and hemiplegias, tabes dorsalis, paralytic dementia

Complementary Examinations

Direct Demonstration of the Etiologic Agent

1. Dark-field examination: its maximum indication lies in primary syphilis. It can be used in papular-erosive lesions of secondary syphilis, but with less positivity due to secondary contamination that such lesions often present and due to the existence of saprophytic treponemas. The possibility of negative results may be related to systemic or local treponemicide medication, nonsyphilitic process, or chancre of more than 3 weeks' evolution. The search can also be performed with silver-stained material by the Giemsa method, China ink, and Levaditti's method [3, 8, 11]. All staining methods are inferior to dark field.

Serologic Tests

(A) Non-treponemal tests detect the presence of nonspecific antibodies in serum. They appear 3–5 weeks after the appearance of protosyphiloma. There are basically two types of test: flocculation (VDRL) and complement fixation test (Wasserman).

(B) Treponemal tests: specific tests based on the detection of antibodies against *T. pallidum*. These tests include direct immunofluorescence (FTA-ABS), *T. pallidum* immobilization (TPI), hemagglutination assay (TPHA), and enzyme immunoassay (EIA) methods [3, 12].

Diagnosis (Box 8.3)

Box 8.3 Types of diagnosis in syphilis patients

Clinical presentation (syndromic diagnosis)

Clinical presentation plus laboratorial examinations (etiologic diagnosis)

Laboratory examinations (diagnosis of latent disease)

Differential Diagnosis

Syphilis can occur concomitantly with other STDs or be confused with them or with similar conditions. Box 8.4 shows the main diseases to be differentiated from acquired syphilis cases.

Box 8.4 Differential diagnosis of acquired syphilis

Stage	Pathologies
Primary	Genital herpes simplex, chancroid, donovanosis, lymphogranuloma venereum, Behçet syndrome, leishmaniasis, genital traumatic lesions, other genital ulcers
Secondary	Viral and drug rashes, Gibert's pityriasis rosea, lichen planus, lymphomas, hanseniasis, sarcoidosis, mucous lesions of pemphigus vulgaris
Tertiary	Malignant tumors, sarcoidosis, tuberculosis, indurated erythema, other neurologic conditions

Therapeutic Approach

T. pallidum is one of the known organisms most sensitive to penicillin, with lesions disappearing in 12–18 h after systemic administration. Thus, the recommended dosage for the treatment of early syphilis is benzathine penicillin 2.4 million IU intramuscularly, repeated after 1 week. In late syphilis the recommended dose is 7.2 million IU intramuscularly given in three doses of 2.4 million IU per week. In cases of allergy to penicillin, the following is recommended: doxycycline 200 mg/day [13, 14] for 15–30 days; erythromycin 2 g/day for 15–30 days; ceftriaxone 1 g/day intramuscularly for 10 days [3, 8]. Clinical and serologic follow-up of syphilis patients is extremely important, especially when they are coinfected with HIV or when using regimens other than penicillin, and serological tests should be carried out at 3, 6, 9, and 12 months after therapy. (see chapter 2).

Chancroid

Epidemiology

Chancroid is a cosmopolitan disease whose prevalence has declined in the United States, with outbreaks in industrialized countries, but with a higher prevalence in Africa, the Middle East, and tropical and subtropical regions of South America, where its incidence may exceed that of syphilis as the cause of genital ulceration. Its occurrence is higher in males.

Etiopathogenesis

Acute infection characterized by genital/anal ulcers that may occasionally occur on the lips, mouth, tongue and oropharynx, with pus and regional invasion of nodes, with likely development of regional, painful adenitis with no systemic manifestations. It results from sexual transmission and is caused by a Gram-negative bacillus called *Haemophilus ducreyi* [3, 8]. It has high infectivity and low pathogenicity. The agent is a Gram-negative, intracellular, facultative anaerobic bacillus of rounded ends and devoid of capsule or motility. It is arranged in single or double chains, in arrangements that resemble a "train track" within polymorphonuclear neutrophils. *H. ducreyi* does not penetrate the intact skin, requiring the presence of solution of continuity for penetration [1, 15].

Clinical Presentation

Chancroid has a short incubation period, of about 2–5 days, after which the first signs of the disease arise, reflected by the presence of a small papule or a vesicopustular lesion that rapidly progresses into an ulcerous, shallow lesion of soft basis, and irregular, undermined, cleanly cut borders (Fig. 8.5), surrounded by an erythematosus live halo and covered with necrotic, purulent, and foul-smelling exudate (Fig. 8.6). The lesions are painful and present in varied numbers and sizes because of its characteristic autoinoculation. Clinically, chancroid can be classified as herpetic, with vesicular or vesicopustular lesions, vesicobullous, follicular, and phagedemic. In men the lesions are more frequently located near the frenulum, balanopreputial sulcus, and glans. In women, disseminated lesions are common, extending from the anus to the vulva. Occasionally the women may be asymptomatic when the ulcers occur in the vaginal wall or cervix. In 50% of cases, uni- or bilateral ganglia infarction occurs, with two-thirds of these progressing to floating

Fig. 8.5 Chancroid with multiple lesions on the penis

Fig. 8.6   Chancroid lesion with erythematous halo

and fistulization, with drainage of purulent material through a single fistula, which can aid in the differential diagnosis with lymphogranuloma venereum. About 5–30% of cases of chancroid can be associated with hard chancre of syphilis, causing ulcerated lesions with clinical features that are common to both diseases (Rollet mixed cancer). Chancroid lesions do not progress to spontaneous healing, and the ulcers of untreated patients can coalesce and lead to the formation of giant ulcerative lesions with deformities and impairment of deep tissue planes, giving rise to local fistulas. After treatment the lesions usually leave small scars after healing [15, 16].

Complementary Examinations (Box 8.5)

Examinations are conducted mainly through direct observation of the agent, whereby after collection of purulent material from the ulcer base, Gram staining is performed for observation of bacilli, which are Gram negative and arranged in a "single line" or "palisade" inside polymorphonuclear neutrophils. Despite being a bacillus of difficult cultivation, culture is the most sensitive method for its identification. The most recommended techniques are Nairobi, Johannesburg, and chocolate agar supplemented with vancomycin. Another diagnostic method is the use of genetic engineering, whereby DNA probes are used to identify the agent. This methodology has shown high sensitivity when

adapted to the polymerase chain reaction (PCR) [15–17]. Methods for antigen detection, molecular biology tests, and serologic tests still cannot be recommended for routine diagnosis due to their high costs.

Box 8.5 Chancroid diagnosis
Lesion: ulcerous, shallow of soft basis, and irregular, undermined, cleanly cut borders, surrounded by erythematosus live halo, and covered with necrotic purulent foul-smelling exudate

Gram staining: Gram negative, arranged in a "single line" or "palisade" inside polymorphonuclear neutrophils

PCR

Diagnosis

Differential Diagnosis

Differential diagnosis should include other genital ulcers of infectious and parasitic origin, including hard chancre, lymphogranuloma venereum, donovanosis, genital herpes simplex, American tegumentary leishmaniasis, paracoccidioidomycosis, and ulcerated lesions of Behcet's syndrome [8, 15, 16].

Therapeutic Approach

The recommended regimens are: azithromycin 1 g orally single dose; ciprofloxacin 1 g/day orally for 3 days; erythromycin stearate 2 g/day orally for 7 days; or ceftriaxone 250 mg intramuscularly, single dose [16–18].

Gonorrhea

Epidemiology

Gonorrhea is one of the oldest morbid states of our civilization. Urethral secretions of venereal origin, supposedly gonococcal, were already

reported by the Chinese during the empire of Huang Ti in 2637 BC [19]. See Box 8.13 for more information.

Etiopathogenesis

Gonorrhea is an infectious, inter-human disease, caused by a Gram-negative diplococcus called *Neisseria gonorrhoeae*, which produces Gram-negative, nonflagellated, nonspore-forming, aerobic, immobile cocci, with a diameter between 0.6 and 1.0 μm. It is an intracellular microorganism devoid of capsule whose incubation time is 3–10 days. Its ability to adhere to the epithelium of the anterior urethra is due to the presence of a filamentary appendix called pilli, which cannot adhere to the keratinized epithelium; therefore, lesions are rarely found in the navicular fossa in men and in the birth canal in women [20]. Approximately 70% of infected women have no symptoms, but only 3% of infected men are asymptomatic.

Clinical Presentation

After an incubation period of 2–5 days after the infectious sexual contact, tingling or intraurethral pruritus and dysuria initially develop, followed by mucosal urethral flow, which quickly becomes mucopurulent, of greenish-yellow color, with abundant and spontaneous clearance (Fig. 8.7). The edges of the urethral meatus in general are erythematous and edematous. As the process extends to the portion of the posterior urethra, suppuration increases as well as symptoms of inflammation with cutting sensation and burning on urination and urinary frequency.

The gonococcal urethritis in women does not have the clinical exuberance of that occurring in men, and the clinical picture usually consists of dysuria, urgency and, less frequently, yellowish secretion. The majority of cases are associated with inflammation of Skene glands [21–23].

The hematogenic dissemination of the gonococcus, usually by chronicity of a localized infection, begins with a bacteremia phase, with general

Fig. 8.7 Gonorrhea

symptoms of fever, arthralgia, and skin lesions characterized by papular pustulas that develop into necrotic, nonconfluent lesions, mainly affecting ends; it can also cause monoarthritis in large joints, and cases of meningitis, endocarditis, and brain processes may occur.

Gonococcal proctitis occurs as a result of anal intercourse, and occasionally in women through contamination by vaginal discharge. It is generally asymptomatic but can cause a burning sensation, pain, and presence of bloody secretion and pus.

Gonococcal oropharyngitis occurs because of the practice of oral sex, and can be found in 10–20% of heterosexual women with gonorrhea and 10–25% of men who have sex with men. It is usually asymptomatic and may result in pharynx erythema or tonsil inflammation, with conditions that range from the presence of purulent secretion to severe ulceration with pseudomembrane and cervical adenopathy [20, 24].

Gonorrhea can be transmitted from an infected mother to a child through the birth canal, and the

child may develop gonococcal ophthalmia which if undiagnosed can lead to vision loss and, if it reaches the brain, encephalitis and death.

Other clinical aspects:

Urologic sequelae

Sequelae include cases of orchiepididymitis (the most common early complication), urethral stenosis (mainly in the distal urethra), balanoposthitis, and prostatitis, usually by ascending route.

Female gonorrhea

The clinical picture in women is oligosymptomatic, with 70% of female cases of gonorrhea being asymptomatic. The canal of the cervix is the primary site of gonococcal infection. In women, cervical infections may be accompanied by vaginal discharge, abnormal vaginal bleeding, and dysuria. The main complications in women include abscess of Bartholin's glands, endometritis and salpingitis, and pelvic inflammatory disease [20–22].

Disseminated gonococcal infection

This results from gonococcal bacteremia. It can originate from infections of the pharynx, urethra, or cervical canal that are often asymptomatic. In dermatitis-arthritis syndrome, the patient has fever, skin lesions characterized as macules or pustules with central necrosis or bleeding in the extensor surface of the limbs and inguinocrural region, and arthralgia affecting the hands, feet, ankles, and elbows. In most cases there is septic arthritis with joint effusion. In 50% of cases, gonococcus can be isolated from the synovial fluid. Meningitis and endocarditis are rare [20, 22].

Complementary Examinations (Box 8.7)

1. Bacterioscopic examination: the presence of Gram-negative diplococci shown in urethral discharge by direct examination, fixed and stained by the Gram method, constitutes a sufficient basis for the diagnosis of gonorrhea [19, 20] (Fig. 8.8)
2. Culture: enriched and selective media are recommended. The selectivity ensures bacteria growth and development, which is often prevented in nonselective media, through the phenomenon of competition offered by other bacteria. Among the selective media, the most traditional are modified Thayer–Martin medium, Martin Lewis agar, and New York City agar [19, 20]
3. Carbohydrate degradation tests: these tests detect the production of acid formed in carbohydrate degradation, and are used when the confirmatory identification of the agent is required. This evidence, as well as its results, is shown in Box 8.6 [19, 20].
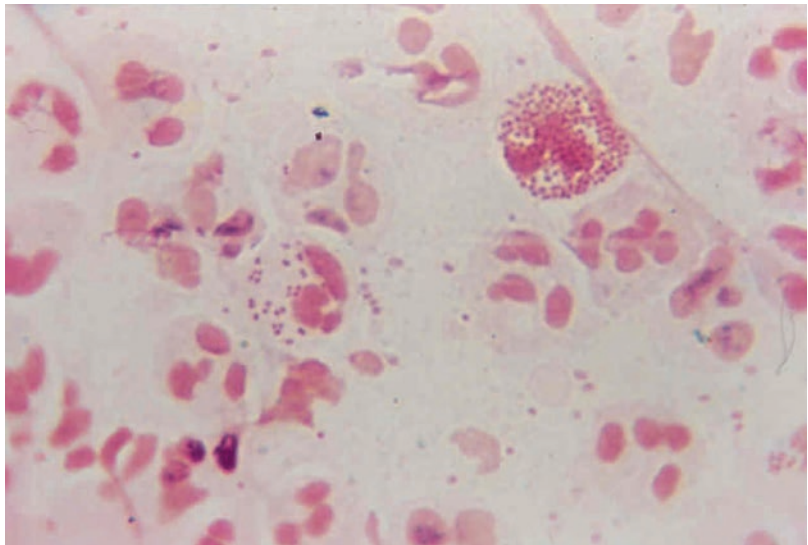
Fig. 8.8 Intracellular Gram-negative diplococcus

Box 8.6 *Neisseria* **carbohydrate degradation tests**

Specimen	Glucose	Maltose	Sucrose	Lactose
Neisseria gonorrhoeae	+	−	−	−
Neisseria meningitidis	+	+	−	−
Neisseria lactamica	+	+	−	+

Box 8.7 Gonorrhea diagnosis

Clinical manifestations: (a) typical mucosal urethral flow (syndromic) and (b) several systemic manifestations (need laboratory examinations)

Basic laboratory examination: Gram-negative diplococci shown in urethral discharge by direct examination

Additional laboratory examination: culture, carbohydrate degradation tests

4. DNA amplification tests: molecular biology techniques, especially PCR and ligase chain reaction (LCR). The LCR has the advantage of being performed with the urine of the patient with a suspicious clinical picture. It is a specific, sensitive, and noninvasive test [25, 26]

Diagnosis

Differential Diagnosis

The main differential diagnosis of gonorrhea is shown in Box 8.8.

Box 8.8 Differential diagnosis of gonorrhea

Causes	Agents
Bacterial	*Chlamydia trachomatis, Ureaplasma urealyticum, Haemophilus vaginalis. Staphylococcus, Streptococcus, Enterococcus*
Parasitic	*Trichomonas vaginalis*
Viral	Herpes simplex virus
Fungal	*Candida albicans*
Chemical	Introduction of irritant substances in the urethra for prophylactic or therapeutic purposes
Metabolic	Diabetes
Traumatic	Habit of expressing the glans for showing secretion (milking)

Therapeutic Approach

The recommended regimens for the treatment of uncomplicated acquired gonorrhea are: ciprofloxacin 500 mg orally, single dose; ceftriaxone 250 mg, intramuscularly, single dose; ofloxacin 400 mg orally, single dose; or spectinomycin, 2 g intramuscularly, single dose [19, 20]. (see chapter 2).

Genital Warts

Epidemiology

See Boxes 8.12 and 8.13.

Etiopathogenesis

Genital warts, or condylomata acuminata, are caused by the human papillomavirus (HPV), which infects the stratified squamous epithelium and causes a variety of skin lesions, secondary to proliferation of squamous cells [27]. HPV infects the epithelia of keratinized and nonkeratinized

surfaces through continuity solutions of the epidermal barrier. Warts are initially located in the basal layer cells, where their proliferation is stimulated by the encoded viral genes and they are transported to the upper layers of the epithelium.

The main HPVs associated with genital warts are 6, 11, 16, 18, 30,31, 34, 35, 39, 40, 42–45, 51–59, 64, 66–68, 70, and 73.

Clinical Presentation

The initial lesion presents as a papular, nonkeratotic lesion with a digitated surface, the color ranging from skin color to dark brown. The lesions can be unique, single, or multiple, and may coalesce and form large vegetating masses. The most common locations are the glans, female external genitalia (Fig. 8.9), balanopreputial sulcus, frenulum, urethral meatus, inner and outer leaflets of the foreskin, penis body (Fig. 8.10), and inguinal fold. Lesions located in the urethral meatus may occur as bright and reddish elevations on the mucosal surface of the anterior urethra. Perianal lesions may be located exclusively in the anus, being associated with anal intercourse. When present in the anal mucosa, the lesions can progress to the rectal epithelium, and

Fig. 8.10 Condyloma acuminatum on the penis

have to be researched by proctoscopy. Occasionally anogenital lesions may acquire large dimensions, resulting in the so-called condyloma of Buschke–Lowenstein, which behaves clinically and histologically as a verrucous carcinoma. Oral condyloma acuminatum mainly affects the lips, gums, and tongue, being more frequent in patients coinfected with HIV [28].

Complementary Examinations (Box 8.9)

In daily practice, the diagnosis has been based on findings of clinical examination or peniscopy

Fig. 8.9 Condyloma acuminatum in female genitalia

associated with biopsies with histopathology, revealing koilocytosis signals. Currently the methods of molecular hybridization, such as hybrid capture and PCR, which are based on viral DNA findings, are being introduced into daily practice [29].

Diagnosis

Differential Diagnosis

Solid exophytic lesions in the genital and perianal regions should be considered in the differential diagnosis of condylomata acuminata, including Tyson's glands, Fordyce granules, lichen planus, lichen nitidus, seborrheic keratosis, epidermal nevus, angiokeratomas, skin tags, and molluscum contagiosum [28].

Therapeutic Approach

The therapeutic approach is not easy and should be focused on the particularities of each case, with no treatment modality being effective in all cases. Clinical and subclinical lesions on the partner should be always looked for, and untimely therapies aimed at faster healing should always be avoided, since they lead to greater morbidity and no increase in efficacy. Therapy may be carried out as follows:

(a) Antimetabolites: 10% or 50% podophyllin in tincture of benzoin with application once a week; podophyllotoxin 0.5% in benzoin tincture, three consecutive days per week;

5-fluorouracil, daily application with removal after 2 h of application.

(b) Caustics: 50–90% trichloroacetic acid once a week; potassium hydroxide 5–10% once a day.

(c) Cryosurgery with liquid nitrogen

(d) Electrosurgery

(e) Immunomodulators: imiquimod 5% cream, three times a week

(f) Keratinization regulators (in extensive cases): retinoids 1 mg/kg/day

Lymphogranuloma Venereum

Epidemiology

Lymphogranuloma venereum (LV) is rare in industrialized countries, but is endemic in parts of Africa, Asia, South America, and the Caribbean [30].

Etiopathogenesis

This is a urogenital tract infectious disease of inflammatory and invasive nature, caused by *Chlamydia trachomatis* serotypes L1, L2, and L3, in contrast to the A–C serotypes of this agent, which cause eye infections such as trachoma, and D–K serotypes that cause genital infections.

Clinical Manifestations

The incubation period ranges from 3 to 30 days [31]. Generally the more acute symptoms occur in males, while late complications are more common among women. It can also present with a variety of acute and late manifestations, including in the form of proctitis or involvement of the anal region, resulting in stenosis and fistulas. Three stages of the disease are identified in the clinical course [31, 32, 33]:

(a) Primary stage: the first clinical lesion is a painless papule that progresses to a small ulcer unnoticed by the patient, healing spontaneously in a few days. At this stage there may be urethral or cervical mucopurulent discharge.

(b) Secondary stage: characterized by acute lymphangitis, with painful lymph nodes of enlarged volume, determining the so-called inguinal syndrome. They appear after 2–6 weeks of the primary lesion leading to femoral or inguinal adenomegaly, usually unilateral, with flotation and that can rupture, leading to the formation of fistulas draining a large quantity of purulent material (Figs. 8.11 and 8.12). Two adenomegalies separated by Poupart's ligament are characteristics of this disease, corresponding to the "Greenblatt sulcus sign." This stage may be associated with fever, arthralgia, and general malaise. This phase may be complicated by the spread of the disease, producing rare syndromes such as hepatitis, pneumonitis, salpingitis, and exceptionally meningo-

Fig. 8.11 Inguinal adenopathy

encephalitis. Men who have sex with men and women after anal intercourse may develop hemorrhagic proctitis in the acute stages of the disease, with symptoms of anal itching, and mucoid and mucopurulent rectal discharge. Proctitis may generate diarrhea, constipation, and tenesmus. The lymph node chain that is specifically affected in this disease is related to the site of primary infection. Primary infections in the penis, anterior urethra, vulva, and anus may be associated with inguinal buboes. On the other hand, the primary infection of the posterior urethra, vagina, cervix, or rectum may lead to the involvement of perirectal lymph nodes or deep inguinal lymph nodes, which are not accessible to palpation during physical examination. The involvement of these nodes will lead to pelvic pain and tenderness in the lower abdomen [32].

(c) Tertiary stage: refers to late complications that affect the rectum and genitals, including elephantiasis (esthiomene). These complications are rare in men except among homosexuals. In the male genitals, elephantiasis can affect only the foreskin, the shaft of the penis and scrotum separately, or all of the external genitalia. The genital tissues become woody and often deformed, and the surface becomes verrucous. The penis can have the shape of a "ram's horn" or saxo-

Fig. 8.12 Bilateral inguinal adenopathy

phone [33]. In women, the progressive and chronic lymphangitis and pelvic and inguinal adenitis can determine chronic edema, sclerosing fibrosis of the subcutaneous tissue, and chronic genital ulceration, called esthiomene. The esthiomene involves the labia, vulva, and clitoris. Genital elephantiasis, of both men and women, is often associated with anorectal complications, including fistula and constrictions [33].

Complementary Examinations (Box 8.10)

The complement fixation test is gender-specific and does not distinguish among species of *Chlamydia*. Thus, a complement fixation titer that is higher than 1:256 strongly suggests the diagnosis of lymphogranuloma, while a titer smaller than 1:32 virtually excludes it, except in the very early stages of the disease. The microimmunofluorescence test is able to distinguish infections of different species of *Chlamydia*. IgG titers higher than 1:128 strongly suggest the diagnosis. *Chlamydia trachomatis* may be isolated in tissue culture using the HeLa-299 strain or McCoy cells, or by direct fluorescence microscopy. PCR or LCR, which detect the specific plasmid or the DNA genome of *C. trachomatis*, are also sensitive methods for the diagnosis [30, 33].

Box 8.10 LV diagnosis

Clinical aspects depend on stage: painless papule, small ulcer, mucopurulent discharge, acute lymphangitis, "Greenblatt sulcus sign," inguinal buboes, esthiomene

Laboratory examinations: complement fixation test, microimmunofluorescence test, culture, direct fluorescence microscopy, PCR, or LCR

Diagnosis

Differential Diagnosis

The differential includes other sexually transmitted diseases such as syphilis, chancroid, gonococcal proctitis, amoebic dysentery, Crohn's disease, ulcerative colitis, anal carcinoma, and donovanosis [32, 33].

Therapeutic Approach

The therapy currently recommended is: tetracycline 1 g/day orally for 21 days; doxycycline 200 mg/day orally for 21 days; erythromycin 2 g/day orally for 21 days [33]. Ciprofloxacin and metronidazole, very useful in Crohn's colitis, are ineffective for lymphogranuloma.

Donovanosis

Epidemiology

Donovanosis is more common in individuals of low socioeconomic status, being endemic in tropical and subtropical countries [37, 38]. The incidence between the sexes varies from study to study, but there seems to be no predilection for gender. It is a disease that affects almost exclusively adults between 20 and 40 years of age. There are no reports of congenital infection, but there are reports of cases in infants and newborns [39]. In children, cases are often associated with contact with infected adults, not necessarily for sexual abuse.

Etiopathogenesis

This is a chronic, progressive, and indolent infectious disease, which mainly affects the skin and mucous membranes of the genital and perigenital areas. Often associated with sexual transmission, it has low infectivity. It is caused

by a Gram-negative coccobacilli, facultative aerobe, which stains more intensely at the ends than in the center, can be encapsulated or not, is intracytoplasmic and immobile, called *Calymmatobacterium granulomatis* [34–36].

Clinical Presentation

The period of incubation is reported as being from 1 to 360 days; however, induced lesions in volunteers suggest a period of 50 days [39].

The disease begins with papules or subcutaneous nodules at the inoculation site, which can develop to superficial ulceration. The ulcers can be of lenticular size, with everted edges and mild inflammatory reaction. Their growth is slow and painless, and they become well-defined, granulomatous, with centrifugal and serpiginous character, bleeding easily. They can be self-inoculated and multiple, with mirror configuration being frequent [39–41]. Generally the balanopreputial sulcus is affected more often (Fig. 8.13), followed by the anus, vaginal fourchette, and cervix.

Typically there is no adenitis in donovanosis. Extragenital lesions are almost always secondary to a genital focus and can affect the lips, gums, buccal mucosa, palate, pharynx, scalp, and chest. Spread into the abdominal cavity (intestine, spleen, liver, uterus, and ovary) is extremely rare and is observed

Fig. 8.13 Nodulo-ulcerated lesion with mirror image

more often in endemic areas. The clinical course involves change in general condition, with fever, anemia, night sweats, weight loss, and toxemia.

Donovanosis has a more aggressive course during pregnancy, and women with atypical lesions on the genitals should have this diagnosis considered in the prenatal follow-up.

Complementary Examinations

Direct microscopy is the fastest and most reliable diagnostic method with the use of Giemsa, Leishman, and Wright staining for the identification of Donovan bodies. Histopathologic examination is useful for cases in which the cytodiagnosis does not allow the confirmation of the clinical suspicion. The agent culture is difficult, and can be performed with cells in monolayers with human monocytes, Hep-2 cells, and mouse peritoneal macrophages [42, 43] (Box 8.11).

Box 8.11 Diagnosis of donovanosis
Lesion: papules or subcutaneous nodules at the inoculation site, superficial ulceration, everted edges, and mild inflammatory reaction. Growth is slow and painless, and they become well-defined, granulomatous, with centrifugal and serpiginous character, bleeding easily.

Direct microscopy (Giemsa, Leishman, and Wright staining): Donovan bodies
Histopathologic examination

Differential Diagnosis

Primary syphilis, chancroid, chronic herpetic ulcers, condyloma acuminatum, lymphogranuloma venereum, squamous cell carcinoma, cutaneous tuberculosis, paracoccidioidomycosis, leishmaniasis, and pyoderma gangrenosum are included in the differential diagnosis [39, 41].

Therapeutic Approach

The following therapy is currently recommended for donovanosis: azithromycin 500 mg/day orally; doxycycline 100 mg twice daily, orally; erythromycin 500 mg four times a day; or sulfamethoxazole/trimethoprim 400/80 mg, two tablets twice daily. Regardless of the treatment regimen, it should be maintained until clinical cure [44, 45].

Considerations of the World Health Organization (WHO) and Centers for Disease Control and Prevention, USA (CDC) About STDs

In Boxes 8.12 and 8.13, we highlight recent quotes from the WHO and CDC, respectively, on STDs.

Box 8.12 WHO comments about STDs [46]
More than 1 million STDs are acquired every day.

The majority of STDs have no symptoms or only mild symptoms that may not be recognized as an STD.

The most common conditions they cause are gonorrhea, chlamydial infection, syphilis, trichomoniasis, chancroid, genital herpes, genital warts, human immunodeficiency virus (HIV) infection, and hepatitis B infection.

More than 290 million women have a human papillomavirus (HPV) infection.

Several STDs, in particular HIV and syphilis, can also be transmitted from mother to child during pregnancy and childbirth, and through blood products and tissue transfer.

Drug resistance, especially for gonorrhea, is a major threat to reducing the impact of STDs worldwide.

When used correctly and consistently, condoms offer one of the most effective methods of protection against STDs, including HIV. Female condoms are effective and safe, but are not used as widely as male condoms by national programs.

Box 8.13 CDC comments about STDs [47]
Check the *Five P's* in STD assistance: *P*artners, *P*ractices, *P*revention of Pregnancy, *P*rotection from STDs, and *P*ast History of STDs

In the United States, an estimated 820,000 new *N. gonorrhoeae* infections occur each year. Gonorrhea is the second most commonly reported communicable disease.

Many cases of HIV infection continue to be diagnosed at advanced stages, as evidenced by low CD4 cell counts.

At the initial HIV care visit, providers should test all sexually active persons with HIV infection for curable STDs (e.g., syphilis, gonorrhea, and chlamydia) and perform testing at least annually during the course of HIV care.

Nongonococcal urethritis: Chlamydial infection is the most frequently reported infectious disease in the United States, and prevalence is highest in persons aged ≤24 years.

HPV causes cervical cancer, which is the fourth most common cancer in women. A large majority (around 85%) of the global burden occurs in the less developed regions, where it accounts for almost 12% of all female cancers.

Pelvic inflammatory disease: sexually transmitted organisms, especially *N. gonorrhoeae* and *C. trachomatis*, are implicated in many cases.

Sexually transmitted gastrointestinal syndromes: include proctitis, proctocolitis, and enteritis. *N. gonorrhoeae, C. trachomatis, T. pallidum*, and HSV are the most common sexually transmitted pathogens involved.

The following routine presumptive treatment after a sexual assault is recommended:

An empiric antimicrobial regimen for chlamydia, gonorrhea, and trichomonas.

- Emergency contraception. This measure should be considered when the assault could result in pregnancy in the survivor.

- Postexposure hepatitis B vaccination (without HBIG) if the hepatitis status of the assailant is unknown and the survivor has not been previously vaccinated.
- HPV vaccination is recommended for female survivors aged 9–26 years and male survivors aged 9–21 years. For MSM with who have not received HPV vaccine or who have been incompletely vaccinated, vaccine can be administered through age 26 years. The vaccine should be administered to sexual assault survivors at the time of the initial examination, and follow-up dose administered at 1–2 months and 6 months after the first dose.

Presumptive treatment for children who have been sexually assaulted or abused is not recommended because (1) the incidence of most STDs in children is low after abuse/assault, (2) prepubertal girls appear to be at lower risk for ascending infection than adolescent or adult women, and (3) regular follow-up of children usually can be ensured. However, some children or their parent(s) or guardian(s) might be concerned about the possibility of infection with an STD.

Check recommendations for postexposure HIV risk assessment of child, adolescent, and adult survivors within 72 h of sexual assault.

Glossary

Condyloma lata A cutaneous manifestation of secondary syphilis and can be misdiagnosed as genital warts. It is characterized by flat plates that occur most often in moist skin areas, especially around the genitals and anus.

Condyloma acuminata Wart-like growths around the anus, vulva, or glans penis. Genital warts are symptoms of a contagious STD caused by some types of human papillomavirus.

Donovan bodies Bacillary intracellular inclusions in macrophages are called Donovan bodies.

Esthiomene A condition in which there is chronic hypertrophy and destructive ulceration of the external genitals of the female. The labia may be enlarged, thickened, and fibrotic. It is analogous to elephantiasis.

Gumma A growth with a firm, necrotic center surrounded by inflamed tissue, which forms an amorphous proteinaceous mass. The central regions begin to die through coagulative necrosis and ulcerate. Other diseases, as well as syphilis, may exhibit gummas.

Rupioid crust The term rupioid has been used to describe cone-shaped plaques with thick, dark lamellate, and adherent crusts on the skin that resemble an oyster or shell.

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Bacterial Infections

Giancarlo Bessa

Key Points Summary
- Pyodermitis is common, accounting for 0.5% of outpatient visits to primary care
- Pyodermitis is predominantly caused by Staphylococcus aureus and group A streptococci, ranging from mild superficial to life-threatening systemic infections
- Superficial manifestations include impetigo, ecthyma, and folliculitis
- Deep and systemic infections include erysipelas, cellulitis, and necrotizing fasciitis.
- Treatment of bacterial skin infections needs to consider clinical manifestations, patient factors, and local current antimicrobial resistance patterns.

Introduction

Bacterial skin and soft-tissue infections (SSTIs), or simply pyodermitis, refer to inflammation of the epidermis, dermis, subcutaneous tissue, or skin appendages caused by invasion by pyogenic bacteria, mainly *Staphylococcus aureus* and *Streptococcus pyogenes* [1, 2]. Sometimes the term

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"pyoderma" is used as a synonym for impetigo, a superficial primary infection of the skin [3].

Pyodermitis can be classified as primary, when affecting healthy skin, or secondary, when the infection occurs on preexisting dermatoses such as dermatitis and infections caused by other agents such as viruses (e.g., herpes simplex) and parasites (e.g., scabies). Reactive skin disease (cutaneous manifestations of infections in other organs) may also occur, usually mediated by toxins [4].

The guidelines of the Infectious Diseases Society of America (IDSA) classify pyodermitis into purulent and nonpurulent and stratify the condition, on the basis of clinical manifestations, as mild, moderate, and severe. Nonpurulent infections include cellulitis and erysipelas, whereas abscesses fall into the purulent category [5].

The definition of complicated SSTIs, widely used in clinical trials, is related to pyodermitis that entails complex management (including surgical procedures and systemic antibiotic treatment), and/or that occurs in patients who have significant underlying comorbidities (such as diabetes and systemic immunosuppression) [6].

Epidemiology

Pyodermitis infections are highly prevalent and represent the most common infection presentation in patients visiting the emergency room in both hospitals and outpatient practices [4].

They account for 0.5% of all outpatient visits to primary care [7]. SSTIs are responsible for about 10% of hospitalizations in North America [8]. The variable clinical presentation of the disease makes it difficult to assess its exact incidence and prevalence, but, in general, the infection is estimated to occur in about 7% of the population [2]. In the past decades a significant growing trend in the incidence of pyodermitis has been observed, both in the community and healthcare settings [9]. This may be explained by the increased number of immunosuppressed patients (e.g., transplant recipients, cancer patients, and AIDS patients), more invasive medical techniques, and increased incidence of surgical wound infections [4].

Etiopathogenesis

SSTIs usually begin with disruption of the skin barrier (Box 9.1), leading to penetration by and proliferation of the infective agent [4]. The infection rarely results from hematogenous spread of bacteria. The skin can also be affected by bacterial toxin production in extracutaneous infections, such as staphylococcal scalded skin syndrome (SSSS) and scarlet fever [1].

Box 9.1. Skin Barrier
Physical protective properties of skin and its relative impenetrability by noxious substances and infectious agents; usually considered a function of keratinized epithelial cells mainly from the stratum corneum.

The skin is colonized by saprophyte bacterial flora that live harmlessly as commensals, which typically consist of Gram-positive cocci (coagulase-negative staphylococci, especially *S. epidermidis* and micrococci), aerobic and anaerobic Gram-positive bacilli, diphtheroids (*Corynebacterium* and *Brevibacterium*), Gram-negative bacteria, and yeasts. The normal flora acts as a competitive inhibitor against the growth of pathogenic microorganisms and also

acts on lipid hydrolysis, producing free fatty acids that are toxic to some bacteria [10].

The progression of pyodermitis and its severity result from the interaction of disorders in protection mechanisms (disruption of the skin barrier: mechanical properties of the stratum corneum, changes in skin "normal flora," and colonization by pathogenic microorganisms), host factors (comorbidities, immunosuppression), and microorganism factors (virulence) [1]. The predominant pathogen in skin infections are Gram-positive cocci; *S. aureus* (Box 9.2) and group A *Streptococcus* (*S. pyogenes*; Box 9.3) are the main etiologic agents [4].

S. aureus is one of the most important bacterial causes of SSTIs [1]. This microorganism is responsible for a wide spectrum of clinical manifestations, ranging from superficial skin infections to severe invasive diseases such as sepsis and septic shock. *S. aureus* can also produce numerous toxins such as cytotoxins, pyrogenic toxin, exfoliative toxin, protease, lipase, hyaluronidase, hemolysin, leukocidin, coagulase, β-lactamases, and others, which are important in the pathogenesis of several pyodermitis presentations [11].

Box 9.2. *Staphylococcus aureus*
S. aureus comprises catalase and coagulase-positive Gram-positive cocci. It is considered a major human pathogen, often involved in cutaneous and systemic infections, and is notable for its ability to develop antimicrobial resistance. Methicillin-resistant *S. aureus* (MRSA) is resistant to many of the antibiotics used to treat ordinary staphylococcal infections, mainly the penicillinase-resistant penicillins (such as oxacillin). MRSA infections acquired in hospitals or other healthcare settings are known as healthcare-associated MRSA (HA-MRSA). MRSA infection that occurs in the community setting, frequently among healthy people, is termed community-associated MRSA (CA-MRSA). HA-MRSA and CA-MRSA have distinctive genetic and antimicrobial susceptibility characteristics.

Colonization is an important step in the pathogenesis of *S. aureus* infection, as nasal carriers and other patients colonized by the agent have been described as risk groups for developing infections [11]. Approximately one-third of the population has *S. aureus* as a transient colonizer in its cutaneous and mucous membrane flora and about 20% is persistently colonized. The remaining 50% appears not to be susceptible, for unknown reasons, to *S. aureus* carriage. The main site where it is found the anterior nasal cavities, although other body sites, such as the perineum and throat, may also be colonized [12]. Many studies have indicated the clinical benefit of mupirocin use for decolonization. A systematic review showed a significant reduction of *S. aureus* nosocomial infections associated with intranasal mupirocin decolonization [13]. The treatment of *S. aureus* infections has been more difficult over time because of its prodigious adaptability and the development of multiple antimicrobial resistance [11].

> **Box 9.3.** *Streptococcus pyogenes*
> Streptococci are catalase-negative, Grampositive bacteria that are arranged in pairs and chains. Group A β-hemolytic streptococci are one of the most important etiologic agents of human and animal infections. They are responsible for disease involving the mucous membranes, tonsils, skin, and deeper tissues and are known for nonsuppurative complications mediated by toxins.

The cutaneous manifestations of infection by *S. pyogenes* (group A streptococci) may also vary from minor superficial infections such as impetigo and erysipelas to severe diseases such as necrotizing fasciitis, which frequently results in death [14]. They are more common in childhood and adolescence, which can be assigned to the fact that successive infections confer lasting and specific immunity against this pathogen. The bacterium is acquired by direct contact, so epidemic infections are more common among people in group situations. Ten percent of the population are asymptomatic carriers, especially in the oropharyngeal region and 1% of individuals harbor it in normal skin [2]. Group A streptococci have adhesins, proteins that play critical role in adherence to the surface of human epithelial cells, and the M protein, which protects against phagocytosis and also increases adherence to epithelial tissues. *S. pyogenes* also develops exotoxins (as streptolysin O) that are toxic to numerous cells and contribute to the virulence of the bacteria [3]. Among human pathogens, *S. pyogenes* stands out for its propensity to cause nonsuppurative diseases. The most documented are rheumatic fever and post-streptococcal glomerulonephritis (PSGN). Cutaneous infections by nephritogenic strains are the major cause of PSGN [15]. Although not common, there is evidence of rheumatic fever caused by group A streptococci impetigo [16].

Diagnosis

The diagnosis of the pyodermitis is essentially based on clinical aspects. Cultural examinations may be necessary to confirm the etiologic agent when there is doubt about the diagnosis or there is suspicion of resistant bacteria. Table 9.1 lists the key points in the clinical diagnosis of pyodermitis.

Table 9.1 Clinical diagnosis of pyodermitis

Impetigo	Nonbullous impetigo: superficial erosions surmounted by honey-color. Systemic symptoms are not ordinarily present
	Bullous impetigo: vesicles and flaccid bullae progressing to erosions covered by dark-brownish crusts rounded by a "collarette" of blister remnants
	In the two variants the coalescence of lesions, central clearing, and peripheral extension can lead to circinate lesions
Ecthyma	Ulcerations with infiltrated violaceous borders, covered by dry, thick, adherent crusts that leave scars after healing, often in legs
	Ecthyma gangrenosum: necrotic skin ulcer in immunosuppressed or neutropenic patients with sepsis caused by *P. aeruginosa*

(continued)

Table 9.1 (continued)

Cellulitis	Tender, warm, erythematous area with edema. Abscess and necrosis can occur
	Erysipelas variant: erythematous plaque with well-demarcated raised borders. Bullae may appear over the lesion
	Systemic symptoms common: fever, chills, regional lymph node enlargement
	More common on face and lower limbs
Folliculitis	Superficial folliculitis: hair-centered pustules
	Deep folliculitis or furuncles ("boil"): tender inflammatory papules or nodules. May result in abscesses formation
Necrotizing infections	Necrotizing fasciitis: rapid progression from mild cutaneous signs such as erythema and edema to necrosis and anesthesia. Severe local pain and systemic toxicity with fever, disorientation, and lethargy. May be polymicrobial, involving a mixed aerobe–anaerobe bacterial flora
	Streptococcal gangrene: when associated with streptococci
	Fournier's gangrene: rapidly progressive form of necrotizing fasciitis of the perineal, genital, or perianal regions

Complementary Examinations

In patients with systemic symptoms, blood tests may be helpful. Leukocytosis with neutrophilia and increased serum C-reactive protein levels, procalcitonin levels, and erythrocyte sedimentation rates suggest a complicated infection [4]. The initial investigation for patients who require admission to hospital should include blood cultures and creatinine, bicarbonate, and creatine phosphokinase levels [1].

The diagnosis of pyodermitis is eminently clinical, but cultural examination may be necessary in some situations: when there is doubt about the diagnosis; when the evolution is not as expected (aggressive course or treatment unresponsive disease); when there is suspicion of resistant bacteria (such as MRSA); and, eventually, in immunocompromised patients.

Surface cultures, such as from swab-collected pus, more frequently do not represent the underlying etiologic agent and generally show colonizing bacteria [6]. Tissue specimens obtained by biopsy of the advancing margin of the lesion are preferred to wound swabs or drainage secretions. If there is no open wound, needle aspiration of fluid may be helpful [4]. Despite the low sensitivity of blood cultures, patients who present with severe infection or sepsis syndrome should have blood samples obtained for culture [17].

Assays of anti-streptolysin O (ASLO) antibodies are of value in the diagnosis of streptococcal pyodermitis (except for superficial infections such as impetigo, for which the ASLO response is weak) [3].

Clinical Presentation Patterns

Impetigo

Impetigo is a contagious superficial skin infection. Poor hygiene conditions constitute a risk factor. Infection is more common in economically disadvantaged children in hot climates [2, 3, 5]. In primary impetigo, which develops in normal (or apparently normal) skin, two clinical patterns are recognized: bullous impetigo and nonbullous impetigo. Nonbullous impetigo lesions can be associated with streptococci, staphylococci, or combination of both. Moreover, it is believed that the etiology of bullous impetigo is predominantly staphylococcal, although there have been reports of streptococci detected in these lesions [18].

In secondary impetigo, bacterial superficial infection occurs on pre-existing skin disease, more commonly dermatitis. In cases of impetiginized dermatoses there is a high prevalence of coinfection by two species of bacteria (*S. aureus* and *S. pyogenes*) [19, 20].

β-Hemolytic group A streptococci are the main etiologic agent of impetigo [21]. Occasionally other groups can be found (e.g., C and G) [5]. Characteristically the incidence of impetigo occurs as outbreaks. In patients with chronic dermatitis, recurrence after treatment is common (about 20% within 1 month), probably due to contact with colonized people [19]. In patients with

chronic disseminated eczematous dermatoses streptococcal impetigo can progress rapidly, culminating with systemic involvement, with the presence of fever, toxemia, leukocytosis, and elevation of C-reactive protein [20].

Impetigo lesions usually occur on exposed areas of the body, most commonly on the face and extremities [5]. The diagnosis is clinical (Table 9.1) and can be aided by bacterioscopic and bacteriologic studies [2]. It is a non-life-threatening infection, but can result in PSGN [3].

Bullous Impetigo

Bullous impetigo is caused by *S. aureus*, which produces an epidermolytic exfoliative toxin associated with the genesis of the blisters. This toxin, when spread hematogenously, is implicated in the pathogenesis of SSSS [22]. It is more common in newborns and infants. Strains of *S. aureus* types 71, 80, and 81 predominate in the genesis of bullous impetigo.

Clinically, bullous impetigo manifests as vesicles that rapidly grow to form flaccid bullae, initially with clear fluid content, progressing to yellowish to purulent secretion. The blister then breaks, leaving erosions covered by dark-brownish crusts surrounded by blister remnants (resembling "cigarette burns") (Fig. 9.1) [5].

Bullous impetigo should be differentiated from bullous drug eruptions, chickenpox, herpes infections, SSSS, and other less common bullous diseases (pemphigus vulgaris, bullous pemphigoid, dermatitis herpetiformis) [2].

Nonbullous Impetigo

Nonbullous impetigo represents 70% of impetigo cases [2]. The etiologic agent can be group A streptococci and *S. aureus* [4]. Clinically it appears as an erythematous macula surmounted by a vesicle which becomes pustulous. These vesicular lesions are evanescent and rarely clinically recognized, and evolve to form characteristic yellowish-brown crusts (Fig. 9.2) [3]. Lymphadenopathy can occur in some cases, but systemic symptoms are not ordinarily present [3, 5]. The differential diagnosis of nonbullous impetigo includes herpes simplex, herpes zoster, and scabies [2].

In the two variants the coalescence of lesions, central clearing, and peripheral extension can lead to a circinate lesion, mimicking superficial fungal infection. Treatment of nonbullous impetigo involves cleaning the lesions, removing crusts, and the use of topical or systemic antibiotics, depending on the extent of disease [2].

Ecthyma

Ecthyma is considered a "deeper" impetigo, reaching the superficial dermis. The main etiologic agents are also *S. aureus* and *S. pyogenes* [5], and it usually represents the evolution from neglected impetigo. The clinical manifestations are ulcerations covered by dry, thick, and adherent crusts (Fig. 9.3). The edges are infiltrated and purplish, resulting in scars after healing. Ecthyma occurs most commonly in patients with poor hygiene, low

Fig. 9.1 Bullous impetigo: most of the lesions are in the form of crusts (Courtesy of UFCSPA Dermatology Service)

Fig. 9.2 Nonbullous impetigo on the face: *yellowish brown* crusts on an erythematous base (Courtesy of UFCSPA Dermatology Service)
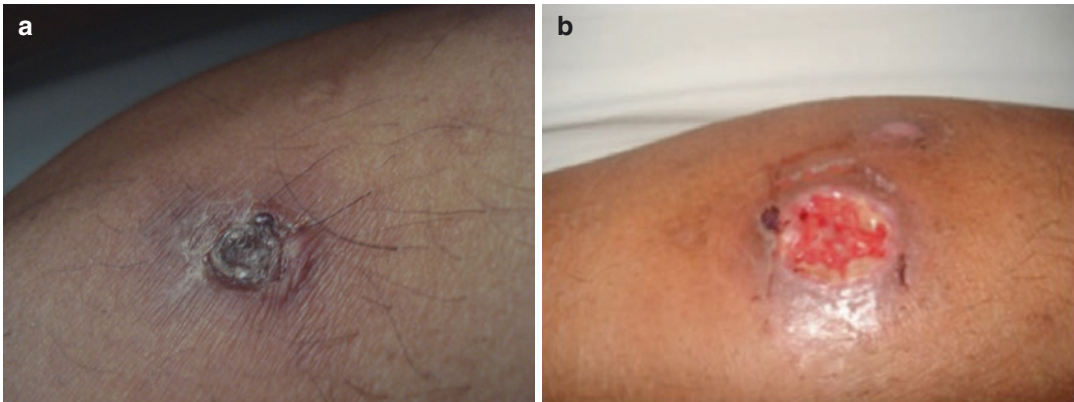
Fig. 9.3 Ecthyma. (**a**) Lesion covered by thick crust. (**b**) Crust removal reveals an ulcer with infiltrated edge (Courtesy of UFCSPA Dermatology Service)

socioeconomic status, malnutrition, and/or immunosuppression [2]. Ecthyma gangrenosum refers to a necrotic skin ulcer that can be a manifestation of secondary infection that sets in typically in the course of sepsis caused by *Pseudomonas aeruginosa*, among transplanted, neutropenic, or diabetic patients [4]. Differential diagnosis should involve ulcerous diseases, such as stasis ulcers and cutaneous leishmaniasis. Often the lesions are multiple and treatment requires systemic antibiotics for at least 10 days [2].

Erysipelas and Cellulitis

Cellulitis is classically defined as an infection involving the dermis and subcutaneous tissues [23]. Erysipelas is a bacterial infection involving superficial dermal structures and is distinguished clinically by its well-demarcated raised borders [24]. However, it is not uncommon that the two patterns coexist in the same patient. In fact, based on clinical overlap and similar bacteriology of the two conditions, cellulitis and erysipelas are now considered manifestations of the same condition, a deep skin infection associated with severe pain and systemic symptoms [25].

The erysipelas variant is almost always caused by β-hemolytic streptococci, from group A (*S. pyogenes*), B, C, or G. An etiologic study that included broad clinical variations of cellulitis patients showed that β-hemolytic streptococci are also the major causative agent in deeper cellulitis and overlapping conditions. More than 80% of the cases were of streptococcal origin, including patients without typical signs of erysipelas, those with purulent drainage, and with comorbidities such as diabetes mellitus [26]. *S. aureus* is also noted to cause cellulitis, especially when associated with furuncles, carbuncles, or abscesses [27]. However, it is important to note that swab culture is not a reliable method to define etiology in cellulitis, as the great majority of cases in which *S. aureus* or Gram-negative bacteria were detected had confirmed or probable β-hemolytic streptococcal disease, diagnosed by combining serology, profound cultures, and response to penicillin treatment [26].

Cellulitis is characterized by local pain, erythema, warmth, edema, and advancing borders [24]. Abscess and necrosis can occur (Fig. 9.4). Erysipelas is a specific type of cellulitis characterized by pronounced superficial dermal inflammation and well-defined raised edges, although in some countries the terms are used as synonyms [28]. The infectious process can lead to the formation of blisters (Fig. 9.5) [29]. The differential diagnosis of erysipelas includes necrotizing fasciitis, contact dermatitis, and deep vein thrombosis [2].

The infectious agent penetrates through skin barrier breaks such as erosions, fissures, and ulcerations [2]. Lymphedema, leg ulcers, toe intertrigo, and traumatic wounds are risk factors for the infection [30]. Patients frequently present with fever, malaise, and leukocytosis, and there is a considerable risk of bacteremia and sepsis [27, 31]. Cellulitis and erysipelas affect mainly women between 40 and 60 years old, having an estimated incidence of between 10 and 100 cases per 100,000 inhabitants per year [32].

Fig. 9.4 Cellulitis: erythematous and edematous lesion, with areas of necrosis and suppuration (Courtesy of UFCSPA Dermatology Service)

Fig. 9.5 Erysipelas bullosa: erythematous plaque with extensive blistering in the lower limb (Courtesy of UFCSPA Dermatology Service)

They can occur on any part of the body, but are more frequent in the face and lower limbs [24].

Treatment is based on a systemic antibiotic, rest, elevation of affected limbs, and local skin care. The conditions that may indicate the need of inpatient treatment include advanced age (>60 years), comorbidities (e.g., immunosuppression, cardiac or renal insufficiency), signs of instability (confusion and hypotension), facial location, or local complications (blisters and necrosis) [33]. In such cases blood cultures are recommended [5].

Recurrence is the main complication of erysipelas and cellulitis, occurring in about 20–30% of cases [2, 30]. An episode of erysipelas in the lower limb may achieve a 46% recurrence rate [34]. Patients with recurrent disease should treat all the predisposing factors for the infection for as long as possible, and may benefit from antimicrobial prophylaxis [24].

Lymphatic involvement can lead to obstruction and damage of the lymphatic system, which predisposes to recurrent infections and leaves some degree of residual chronic swelling. This lymphedema gradually increases the volume of the affected limb, resulting in skin tightening, lipodermosclerosis, and verrucous hyperkeratosis, a condition known as elephantiasis nostra [34].

Staphylococcal Scalded Skin Syndrome (SSSS)

Also known as Ritter disease, SSSS is caused by exfoliative exotoxins (mainly types A and B) produced by *S. aureus* phage group 2 [35]. The major incidence is in infants and small children, with 98% of cases occurring in children 6 years old or younger. When it affects adults it is generally associated with immunosuppression and renal insufficiency [2].
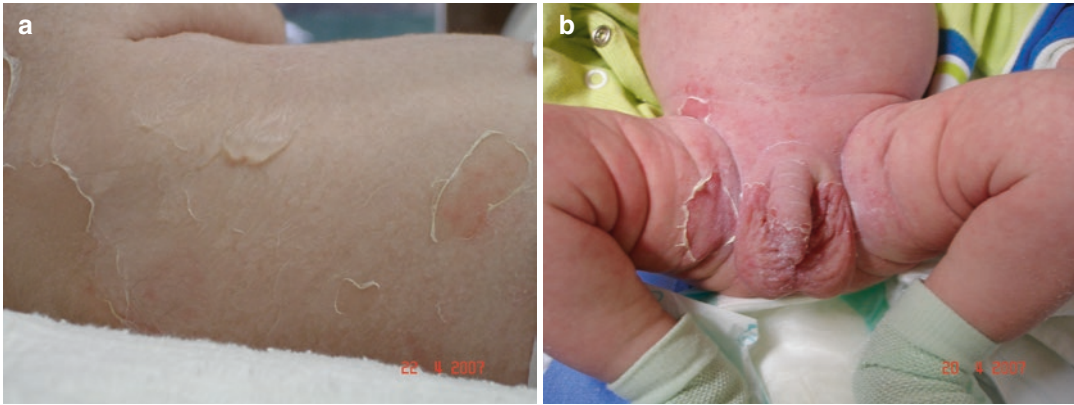
Fig. 9.6 Staphylococcal scalded skin syndrome. (**a**) Flaccid bullae and diffuse detachment of the epidermis. (**b**) Erosions after blister rupture (Courtesy of Dr. Gislaine Olm)

The disease usually begins a few days after pharyngitis, conjunctivitis, otitis, or other staphylococcal infections. The exotoxin produced by about 5% of strains of *S. aureus* is a serine protease that reaches the granular layer of the epidermis, joining desmoglein-1. These toxins are spread hematogenously, causing diffuse epidermal damage [35].

Clinically there is widespread erythema and fever, which starts after the staphylococcal infection. Within 24–48 h large and flaccid bullae develop with epidermal high cleavage and positive Nikolsky sign (Box 9.4). Rupture of the blisters results in large areas of erosions surrounded by epidermal patches (Fig. 9.6). There is no mucosal involvement [2].

The diagnosis is made by clinical observation, isolation of an exfoliative toxin producer *Staphylococcus* strain at the site of primary infection (the blisters are usually sterile), and characteristic histopathology (intraepidermal cleavage at granulosa layer). SSSS should be distinguished from life-threatening toxic epidermal necrolysis [35].

Treatment involves systemic antistaphylococcal antibiotic therapy, fluid and electrolyte control, and local care of eroded areas, with special bandages, dressings, and barrier creams. Re-epithelialization is usually rapid, occurring within 7–10 days of treatment. The mortality rate in infants and small children is approximately 4%; in adults, more than 60% [36].

Box 9.4. Nikolsky Sign

An important semiologic sign named after Pyotr Nikolsky, a Russian physician. The cutaneous rubbing of an apparently normal skin area results in the separation of part or whole epidermis. It is characteristic of acantholytic diseases, i.e., congenital or acquired diseases that compromise adhesion between keratinocytes. The prototype is pemphigus vulgaris and other autoimmune bullous diseases.

Folliculitis

The term folliculitis refers to inflammation of the hair follicle that may be caused by trauma (most commonly friction and depilation), chemical irritants, follicular obstruction and infectious agents. Infectious folliculitis is most commonly caused by *S. aureus*, and is probably the most common skin infection. Other infectious agents, including fungi, may be involved, particularly in immunosuppressed patients. Folliculitis can be classified according to the depth of the infectious process [24].

Superficial folliculitis: The most common form of folliculitis. Inflammation occurs in the upper portion of the follicle, and pus formation is restricted to the epidermis [2]. The initial lesion is a hair-centered pustule, which then forms crusts and heals without scarring. Lesions may be numerous and are located especially in the scalp, neck, buttocks, and extremities. Superficial bacterial folliculitis typically resolves spontaneously and should be distinguished from folliculitis by distinct etiologic agents (such as commensal yeasts) and from other follicular eruptions (such as acne). The use of topical antibiotics can accelerate the healing process [7].

Deep folliculitis or furuncles ("boils"): The infectious process extends through the dermis and involves perifollicular tissues, which usually destroy the hair follicle. It manifests clinically as tender inflammatory papules or nodules. The suppuration process extends to deep dermis and subcutaneous tissue may result in the formation of abscesses [5]. Carbuncles are furuncle aggregates that form broad, swollen, erythematous, deep, and painful inflammatory masses that usually have multiple pus-draining points (Fig. 9.7). In such cases there may be constitutional symptoms such as fever and prostration [24]. Most large furuncles and all carbuncles should be treated with incision and drainage. Systemic antimicrobials are usually unnecessary unless fever or other evidence of systemic infection is present [5].

Folliculitis decalvans: A form of chronic deep folliculitis of the scalp, usually associated with *S. aureus*. The inflammation process leads to follicle destruction, resulting in permanent scarring alopecia. It occurs most commonly in middle-aged men and there is a suspicion that diabetic patients are more susceptible. Differential diagnoses should include cicatricial alopecias in general, dissecting folliculitis, discoid lupus erythematosus, and tinea favosa [2].

Dissecting cellulitis: Also referred to as perifolliculitis capitis abscedens et suffodiens, this manifests with perifollicular pustules, nodules, abscesses, and sinuses that evolve into scarring alopecia (Fig. 9.8). It occurs predominantly in black men between 20 and 40 years old. The course is chronic and multiple treatment options have variable efficacy [37].

Acne keloidalis nuchae: Another clinical pattern which occurs in the lower occipital region in postpubertal black men and also can lead to scarring alopecia with keloid formation. The cause is unknown, but it has been recognized that it may

Fig. 9.7 Carbuncle: aggregates of multiple deep folliculitis, forming an erythematous edematous plaque with multiple points of purulent drainage (Courtesy of UFCSPA Dermatology Service)

Fig. 9.8 Dissecting cellulitis: nodules and sinuses with scarring alopecia

be precipitated by short-cut hair in the nuchal region and probably caused by recurving, ingrowing hair shafts [38]. The bacterial populations identified seem to be a secondary phenomenon. Treatment is difficult. Acne keloidalis is now considered a primary form of scarring alopecia, so therapies found to be useful in other forms of inflammatory scarring alopecia may be prescribed in the treatment of this disease [39].

Sycosis: Deep folliculitis of the beard region, caused by *S. aureus*, which if left untreated becomes chronic. Extensive disease is treated with oral antibiotics such as cephalexin until all signs of inflammation have disappeared. Relapses are not uncommon. The main differential diagnosis is made with dermatophyte folliculitis of the beard region [2].

Cutaneous Abscesses

Defined as pus collections in dermis or deeper tissues, cutaneous abscesses are usually painful and manifest clinically as warm palpable erythematous and edematous floating nodules.

Abscesses are typically a polymicrobial infection, although *S. aureus* is implicated in most cases [5]. The Panton-Valentine leucocid in gene has been associated to the appearance of abscesses, necrotic cutaneous lesions and furuncles caused by MRSA [40]. They may occur after deep inoculation of the infectious agent (penetrating trauma, catheters); as a secondary infection of cutaneous cysts, and as a complication of several pyodermitis conditions, such as cellulitis and deep folliculitis [41]. The treatment of cutaneous abscesses mainly involves surgical drainage of pus [5]. A systematic review found that primary closure after incision and drainage of abscesses is an alternative mode of therapy that may result in faster healing and lower recurrence rates compared with secondary closure [41]. Incision and drainage alone (in the absence of antimicrobial therapy) is generally sufficient for healthy patients with small solitary abscesses (<2 cm) without surrounding cellulitis or systemic symptoms [5].

Necrotizing Infections

Many specific variations of necrotizing soft tissue infections have been described based on multiple criteria (etiology, microbiology, and specific anatomic location). Nevertheless, the initial approach to diagnosis and treatment (antimicrobial and surgical interventions) is similar for all forms and is more important than determining the specific variant [5].

Necrotizing fasciitis is a deep life-threatening infection that extends rapidly along the superficial fascia and subcutaneous tissue planes [42]. It usually develops from an initial break in the skin related to trauma or surgery, and extension from a skin lesion is seen in most cases. Examination of the local site may reveal cutaneous erythema, edema, and discoloration or gangrene and anesthesia (Fig. 9.9). As it progresses there is systemic toxicity, often with fever, disorientation, and lethargy [5]. Paucity of cutaneous findings early in the course of the disease can delay the diagnosis, which correlates with a poor outcome, leading to major tissue destruction, sepsis,

Fig. 9.9 Necrotizing fasciitis: this ecchymosis-like lesion was hard on palpation and quickly evolved to necrosis

multiple organ failure, and death [1]. The infection can be monomicrobial (usually by streptococci, when it may be named "streptococcal gangrene") or polymicrobial, involving a mixed aerobe–anaerobe bacterial flora [4]. Plain radiographs, computed tomography, or magnetic resonance imaging may help in the diagnosis [1].

Fournier's gangrene is a rapidly progressive form of necrotizing fasciitis of the perineal, genital, or perianal regions. The mean age at onset is 53–55 years and the majority of patients have significant underlying diseases, particularly diabetes mellitus [43].

Prompt surgical debridement is the primary therapeutic intervention for necrotizing infections [5]. Appropriate antibiotics, fluid and electrolyte management, and analgesia are mainstays of therapy [1].

Differential Diagnosis

The differential diagnosis of pyodermitis varies according to the clinical pattern (see the preceding sections).

Therapeutic Approach

The empiric choice of antimicrobial therapy must cover the most likely organisms implicated in the infection, so it is important to consider clinical and epidemiologic information [4]. In general, the systemic treatment of pyodermitis, when there is no significant suspicion of MRSA, is made with empiric prescription of penicillinase-resistant penicillins, first-generation cephalosporins, clindamycin, or trimethoprim-sulfamethoxazole (TMP-SMX) [1]. The treatment of severe infections caused by MRSA is traditionally done with intravenous glycopeptides (vancomycin and teicoplanin) or more recently introduced options such as linezolid, daptomycin, and tigecycline. For outpatient treatment of MRSA infections TMP-SMX and tetracyclines can be employed with low clinical failure rates [44, 45]. When there

is a suspicion of polymicrobial infections such as abdominal surgery wound infections; proximity with the genitourinary tract, infection associated with animal or human bites, or, in cases of children under 3 years old, diabetic or immunocompromised patients, it is recommended to administer antibiotics with spectrum against Gram-negative bacteria, such as second-, third-, or fourth-generation cephalosporins, β-lactams associated with β-lactamase inhibitors, or fluoroquinolones [1, 24].

In systemic antimicrobial treatment, the choice between oral or parenteral therapy is generally suggested by the severity of the infection. Parenteral therapy is preferred when the infection is rapidly spreading and significant comorbidities are present [4]. Topical antimicrobial drugs are reserved for the treatment of superficial uncomplicated pyodermitis (namely localized impetigo or impetiginized lesions). In this context, they have some advantages: low risk of systemic adverse effects, high local concentrations, and low cost [46]. A systematic review concluded that mupirocin and topical fusidic acid are equally, or more, effective than oral treatment for localized impetigo, being considered drugs of first choice for treating this condition [47]. More recently, retapamulin, described as a new topical antibiotic to treat cases of impetigo, was recommended for topical application twice daily for 5 days [48]. In clinical trials the efficacy of retapamulin was noninferior to sodium fusidate for impetigo [49] and noninferior to oral cephalexin for secondarily infected superficial wounds caused by trauma [50]. It has not been compared with mupirocin.

In cases of ecthyma or impetigo with numerous lesions, or in outbreaks affecting several people, oral antibiotic therapy is recommended. The antimicrobial agent must be active against *S. aureus* unless cultures yield streptococci alone (when penicillin is the recommended agent). Because most *S. aureus* isolates are methicillin susceptible, dicloxacillin or cephalexin is recommended. When MRSA is suspected or confirmed, a tetracycline, clindamycin, or TMP-SMX is recommended [5].

For the treatment of erysipelas and cellulitis, a systematic review was unable to define the best antimicrobial regimen because there were no two trials that investigated the same antibiotics and there was no standard treatment regimen used as a comparison. The authors concluded that no single treatment was clearly superior, and the recommendations are mostly based on single trials [25]. The IDSA recommends that typical cases of cellulitis without systemic signs of infection should receive an outpatient-based treatment, with an antimicrobial agent that is active against streptococci. For cellulitis with edema, poor defined edges, and systemic signs of infection, many clinicians include an antibiotic with coverage against MSSA, despite the weak evidence to support this. When cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, injection drug use, purulent drainage, or severe systemic symptoms, vancomycin or another antimicrobial drug effective against both MRSA and streptococci is recommended [5]. Small studies support that 5 days of treatment may be as effective as 10 days [25], but treatment should be extended if there are signs of persistent infection [5].

There is evidence that prophylactic antibiotics may reduce recurrence rates of cellulitis or erysipelas in persons with previous episodes. However, the ideal type, dosage, and duration of antibiotics, as well as the group of patients who will benefit most from prophylaxis, were not determined [51]. The IDSA recommends that the prescription of oral penicillin or erythromycin, or intramuscular benzathine penicillin, every 2–4 weeks should be considered in patients who have three to four episodes of cellulitis per year despite treatment of predisposing conditions [5].

For mild, moderate, and severe purulent infections, incision and drainage of the site of infection are considered the milestone of the treatment [6]. The addition of systemic antibiotics to incision and drainage of cutaneous abscesses may improve cure rates in certain circumstances, particularly the use of anti-MRSA antibacterials in settings where MRSA is prevalent [52, 53]. In addition, systemic antibiotics are frequently needed in cases of multiple lesions, associated cellulitis, or

gangrene, in immunosuppressed patients or in the presence of systemic symptoms [5].

Necrotizing infections require aggressive treatment and early prescription of broad-spectrum antibiotics in combination with surgical debridement and hemodynamic support [1]. Empiric antimicrobial treatment should include antibiotics effective against both aerobes, including MRSA, and anaerobes: vancomycin, linezolid, or daptomycin combined with piperacillin-tazobactam, a carbapenem, ceftriaxone plus metronidazole, or a fluoroquinolone plus metronidazole [5].

The emergence of bacterial strains with resistance to multiple agents has complicated the choice of empiric therapy [1]. Many cutaneous infections are caused by MRSA [54]. Macrolide resistance among group A and group B streptococci has also risen, but organisms have remained susceptible to penicillins and cephalosporins [4]. Moreover, the increasing prevalence of infections by multidrug-resistant bacteria is associated with significantly increased morbidity, mortality, and length of hospital stay and costs, compared with infections by susceptible strains [9]. It is therefore important that a local knowledge of the epidemiology and susceptibility of pathogens guides the development of antibiotic guidelines for empiric treatment [1, 33, 55].

Glossary

Abscess Pus collections in dermis or deeper tissues.

Acne keloidalis nuchae A chronic pattern of deep folliculitis of the scalp that occurs in the lower occipital region and leads to scarring alopecia with keloid formation.

Bacteremia Presence of viable bacteria in the bloodstream.

β-lactams A class of broad-spectrum antibiotics, such as the penicillins and the cephalosporins, that chemically contain a β-lactam ring.

Carbapenems A class of β-lactam antibiotics highly resistant to β-lactamases.

Carbuncles Furuncle aggregates that form large, painful inflammatory masses.

Ceftriaxone A third-generation cephalosporin (antibiotic).

Cellulitis Deep skin infection that involves the dermis and subcutaneous tissue associated with severe pain and systemic symptoms.

Cephalexin A first-generation cephalosporin (antibiotic).

Cephalosporins A class of β-lactam antibiotics originally isolated from the fungus *Cephalosporium acremonium*. Successive generations have different antimicrobial spectra: the newer are more active against Gram-negative bacteria.

Clindamycin A semisynthetic antibiotic, derived from lincomycin and active against Gram-positive and anaerobic bacteria.

Daptomycin A cyclic lipopeptide parenteral antibiotic with bactericidal activity against a wide range of Gram-positive bacteria, including *S. aureus* resistant to methicillin and vancomycin. The mechanism of action involves disruption of the bacterial cytoplasmic membrane and inhibition of protein and nucleic acids synthesis.

Dicloxacillin A semisynthetic penicillinase-resistant penicillin.

Dissecting cellulitis Also known as perifolliculitis capitis abscedens et suffodiens, it is a clinical form of chronic folliculitis of the scalp that manifests with pus collections, sinuses, and scarring alopecia.

Ecthyma Bacterial skin infection that reaches the superficial dermis. The main etiologic agents are *S. aureus* and *S. pyogenes*.

Elephantiasis nostra Chronic lymphatic swelling of lower limbs leading to skin tightening and hyperkeratosis, induced by recurrent erysipelas that damage lymphatic vessels.

Erysipelas Deep skin infection considered a specific type of cellulitis that involves superficial dermal structures and is distinguished clinically by its well demarcated raised borders.

Erythromycin A macrolide antibiotic, obtained from the actinomycete *Streptomyces erythraeus*.

Fluoroquinolones A subgroup of quinolones, antibiotics with broad spectrum of antimicrobial activity that inhibit bacterial DNA gyrase.

Folliculitis Inflammation of the hair follicle, associated with multiple causes. Infectious folliculitis is most commonly caused by *S. aureus*. It can be classified into superficial and deep folliculitis.

Folliculitis decalvans Specific form of chronic deep folliculitis of the scalp usually associated with *S. aureus* and leading to scarring alopecia.

Fournier's gangrene A clinical form of necrotizing fasciitis of the perineal, genital, or perianal regions.

Furuncle Also known as a "boil," the deep form of folliculitis that manifests clinically as tender inflammatory papules or nodules.

Fusidic acid Antibiotic derived from the fungus *Fusidium coccineum* that interferes with the bacterial protein synthesis by preventing translocation elongation factor G (EF-G) of the ribosome. It is only active against Gram-positive bacteria such as *Staphylococcus* and can be topically or systemically administered.

Impetigo Bacterial skin infection limited to the superficial layers of the epidermis, caused by *S. aureus* and *S. pyogenes*.

Intertrigo An inflammatory process in skin folds, induced or aggravated by heat, moisture, maceration, friction, and microbial proliferation.

Linezolid A synthetic antibiotic of the oxazolidinone class that prevents formation of essential component of bacterial protein synthesis.

Lymphedema Accumulation of lymphatic fluid in the interstitial tissues of the body with accompanying swelling, often of the extremities, caused by damage in lymphatic vessels or lymph nodes.

Macrolide A class of broad-spectrum antibiotics that chemically contain a large lactone ring and act by inhibiting protein synthesis.

Metronidazole A synthetic antiprotozoal and antibacterial drug that is effective against obligate anaerobes.

Mupirocin Topical antibiotic with bactericidal activity, derived from *Pseudomonas fluorescens*. Its particular mechanism of action results from inhibition of transfer RNA and is not related to any other antibacterial. It is indicated for the treatment of skin infections by Gram-positive organisms, especially *S. aureus*, and is often formulated in cream or ointment at 2%.

Necrotizing fasciitis Deep bacterial infection that extends rapidly along the superficial fas-

cia and subcutaneous tissue planes, resulting in soft tissue necrosis and systemic toxicity.

Penicillins A class of β-lactam antibiotics that were originally isolated from the fungus of the genus *Penicillium* and later gave rise to the various semisynthetic antimicrobials.

Piperacillin-tazobactam A β-lactam antibiotic associated with a β-lactamase inhibitor.

Poststreptococcal glomerulonephritis (PSGN) Acute glomerulonephritis (glomeruli inflammation) following streptococcal infection and characterized by sudden appearance of hematuria, proteinuria, edema, and hypertension.

Retapamulin Topical antibiotic with in vitro and in vivo activity against *S. aureus* (including MRSA) and *S. pyogenes* and poor activity against Gram-negative bacteria. It is a semisynthetic derivative of pleuromutilin compound derived from the fungus *Clitopilus passeckerianus* and inhibits bacterial protein synthesis, but binds at a different site on the 50S subunit of the bacterial ribosome.

Rheumatic fever Inflammatory systemic disease induced by toxins produced by certain strains of group A streptococci. The most characteristic findings are fever, migratory arthritis, neurologic manifestations, and permanent damage to the heart structures.

Ritter disease Also known as staphylococcal scalded skin syndrome, it is characterized by diffuse epidermal detachment caused by exfoliative exotoxins produced by *S. aureus*.

Scarlet fever A bacterial illness that develops in some people who have strep throat. Also known as scarlatina, scarlet fever features a bright red rash that covers most of the body. Scarlet fever is almost always accompanied by a sore throat and a high fever.

Sepsis Systemic inflammatory response to infection.

Staphylococcal scalded skin syndrome (SSSS) See "Ritter disease."

Streptolysin O A hemolysin produced by β-hemolytic streptococci. The laboratory titration of anti-streptolysin O antibody (ASLO) are used as a diagnostic tool of recent streptococcal infection.

Sycosis Etymologically the term refers to an inflammatory process in hair follicles. However, it is most commonly used to describe a chronic deep folliculitis, most commonly in the beard region, caused by staphylococcal infection.

Teicoplanin A glycopeptide antibiotic highly effective against Gram-positive bacteria, especially against staphylococci.

Tetracyclines A class of antibiotics effective against a wide variety of organisms, acting by inhibiting protein synthesis.

Tigecycline The first drug in the glycylcycline class of antibiotics, which acts by inhibiting protein synthesis.

Trimethoprim-sulfamethoxazole (TMP-SMX) Also known as co-trimoxazole, it is a broad-spectrum combination antibiotic. The drug combination is synergistic as the drugs interfere with two successive steps in the formation/utilization of folic acid by microorganisms.

Vancomycin A glycopeptide antibiotic highly effective against Gram-positive bacteria, especially staphylococci.

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Viral Infections

10

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Key Points

- Cutaneous viral diseases comprise a heterogeneous group of diseases with different degrees of severity, ranging from a self-limited course to chronic and recurrent infection.
- The main goal of treatment is to control the outbreak, not to eradicate the virus.
- The severity of disease is related to the immune status of the affected individual.

Human Herpesvirus

Herpesviridae is a large family of viruses, also known as herpesviruses. The Herpesviridae family involves viruses that share a common virion structure. The viral particle consists of a double-stranded DNA core surrounded by an icosahedral capsid consisting of 162 capsomeres surrounded by unstructured protein matrix called tegument,

which in turn is surrounded by a lipid bilayer membrane called the envelope [1].

All herpesvirus infections share the same sequence: primary infection, latency, and reactivation, which, depending on the virus, can be localized or systemic. Some of them may be carcinogenic.

The human herpesviruses discussed in this chapter are described in Table 10.1.

Herpes Simplex (HHV-1 and HHV-2)

Epidemiology

Herpes simplex virus (HSV) comprises Herpesviruses 1 and 2. The seroprevalence in adults in the fourth decade of life for the two types of HSV reaches 90% of the world population, influenced by factors such as sex, age, and geographic location, and is higher in populations of lower socioeconomic status. HSV-1 is predominantly related to orolabial infections (80–90% of cases) and HSV-2 is mostly associated with genital infections (70–90%), although HSV-1 is entailing larger proportions of these infections and becoming more prevalent than HSV-2 in regions such as the United States and United Kingdom [2]. Worldwide HSV-1 prevalence varies with age, race, geographic location, and socioeconomic status; a higher rate of seropositivity has been reported for less industrialized countries. Risk

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Table 10.1 Human herpesvirus

Human herpesvirus	Synonyms	Classification	Main clinical presentation
Human herpesvirus 1 (HHV-1)	Herpes simplex virus type 1 (HSV-1)	Alphaherpesvirinae	Orolabial herpes
Human herpesvirus 2 (HHV-2)	Herpes simples virus type 2 (HSV-2)	Alphaherpesvirinae	Genital herpes
Human herpesvirus 3 (HHV-3)	Varicella zoster virus (VZV)	Alphaherpesvirinae	Varicella and herpes zoster
Human herpesvirus 4 (HHV-4)	Epstein–Barr virus (EBV)	Gammaherpesvirinae	Infectious mononucleosis
Human herpesvirus 5 (HHV-5)	Cytomegalovirus (CMV)	Betaherpesvirinae	–
Human herpesvirus 6 (HHV-6)	–	Betaherpesvirinae	Exanthema subitum
Human herpesvirus 7 (HHV-7)	–	Betaherpesvirinae	Exanthema subitum/ Pityriasis rosea
Human herpesvirus 8 (HHV-8)	Kaposi sarcoma–associated herpesvirus (KSHV)	Gammaherpesvirinae	Kaposi sarcoma

factors for genital HSV infection include older age, female gender, poor socioeconomic status, low level of education, prior sexually transmitted disease (STD), early age at first intercourse, and a higher number of sexual partners over the lifetime [3].

Etiopathogenesis

HSV-1 and HSV-2 are enveloped alphaherpesviruses with double-stranded DNA. They are transmitted through direct contact with active lesions or through mucocutaneous secretions of asymptomatic individuals in the replicative phase of the virus, infecting mucous membranes or small abrasions on the skin [3]. HSV replicates on the inoculated surface, then follows the sensory nerves toward the dorsal nerve root, where it becomes latent. The virus remains dormant and is not removed from the body, and can remain so throughout the life of the infected individual or reactivate intermittently, depending on the cellular immunity that controls the replication of the virus. Possible triggers of relapse episodes are emotional stress, fever, tissue damage at the site of appearance of the lesion, immunosuppression conditions, and ultraviolet radiation. Serious systemic recurrence of clinical infection may occur in immunosuppressed patients [2]. HSV-1 is mainly related to oral, oropharyngeal, facial, eye, and brain lesions, whereas HSV-2 is mainly

responsible for anogenital infections, important for sexual transmission.

Clinical Presentation

The clinical presentations result from the episode of primary infection or recurrence, noting that most primary infections occur asymptomatically.

Two types of initial symptomatic presentations are possible for HSV infection. A true primary HSV infection refers to the first episode of herpes in an HSV-1- or HSV-2-seronegative individual. A nonprimary infection refers to acquisition of one type of HSV by a person already infected with the other type. True primary infections are more severe, often associated with constitutional signs and symptoms as well as longer duration of viral shedding. Analysis of acute and convalescent sera for anti-HSV antibodies is helpful in the differentiation of primary from nonprimary herpetic infections. More specifically, high levels of immunoglobulin (Ig) M are consistent with a primary infection whereas elevated, acute levels of IgG are suggestive of a nonprimary infection.

Lesions of herpetic infection are generally preceded by an incubation period of about 3–7 days, after which a painful cluster of vesicles on an erythematous base appear at the injection site, progressing to erosions, pustules, and crusting, which resolve in about 2–6 weeks (Figs. 10.1

and 10.2). Lesions may be preceded by fever, local lymphadenopathy, and symptoms of pain or numbness at the site where the vesicles appear. In childhood, it is common for a form of primary infection to manifest as herpetic gingivostomatitis, whereby quite painful eroded and edematous lesions on the lips, oral cavity, and oropharynx occur and can cause major drooling and dysphagia. In young adults, it can also sometimes appear as pharyngitis similar to mononucleosis. In geni-

tal herpetic primary infection in women, vulvitis or vaginitis, or injuries to the perineum or even the cervix, can occur. In men, the lesions are located on the penis (glans or body) and in the perineal region (Fig. 10.3).

After primary infection the virus becomes latent, and there may be clinical or subclinical reactivations, and in both the virus can be transmitted [4]. The symptomatic episodes usually have lesions similar to those of the primary infection, but prodromal symptoms of pain or numbness can also occur in the location, although generally the clinical presentation is less extensive and symptomatic, and less durable. Despite the higher prevalence of the disease in orolabial and anogenital regions, the infection can occur in any region of skin or mucous membranes. Infection by either of the HSVs does not generate immunity to protect from infection by the other HSV.

Some special forms of herpetic infection are described below.

- In immunocompromised patients, the lesions may present as extensive ulcerations, and vegetative and exophytic lesions, and may affect

Fig. 10.1 Oral primary HSV infection

Fig. 10.2 Genital primary HSV infection

Fig. 10.3 Recurrence of genital HSV

more than one location or even be disseminated. There may be gastrointestinal and respiratory tract involvement.

- Herpetic whitlow occurs in children or professionals in the medical and dental fields after direct digital contact with infected individuals without the use of gloves. It presents vesicular lesions in the fingers, with pain and swelling (Fig. 10.4).
- Herpes gladiatorum is the term used for infection that occurs in athletes participating in contact sports, such as fights, with injuries in different places of the body where the contact and viral inoculation occurred.
- Eczema herpeticum (Kaposi varicelliform eruption) is a complication that usually occurs in patients with atopic dermatitis, but also in patients with other diseases of compromised skin barriers, such as pemphigus, Darier's disease, Hailey–Hailey disease, burns, ichthyosis, or mycosis fungoides. It is more often apparent on the face, characterized by HSV-1-related eroded and crusty lesions, these being more evident than the vesicles; an overlap of the bacterial infection on the clinical presentation or spread of HSV can occur.

Fig. 10.4 Herpetic whitlow

- Erythema multiforme has HSV as one of the main triggers, accounting for about 80% of recurrent cases. The target lesions, especially in the legs and arms, appear approximately 10 days after viral reactivation and last about 2 weeks. There are generally no associated systemic symptoms [3].
- Extracutaneous forms, such as an eye infection, can cause keratoconjunctivitis and may lead to ulcers and corneal scarring with consequent blindness, and herpes encephalitis, which can have high mortality and morbidity with neurologic sequelae in survivors.

- Neonatal infection presents a higher risk in pregnant women who acquire the infection in the genital area in the peripartum period, with a low risk in cases of recurrent genital herpes. The clinical presentation starts at around 5 days of newborn life, with localized or disseminated lesions, more on the scalp and trunk, and there may be ocular, oral cavity, or multiple organ involvement, much like the central nervous system (CNS). Mortality is high without treatment (>50%), and in survivors the occurrence of neurological and/or ocular sequelae is common.

Diagnosis

In most cases, the diagnosis is based on the patient's history and the clinical signs and symptoms. Laboratory confirmation, however, may be required in immunocompromised patients if the clinical presentation is atypical [5].

Viral etiology can be confirmed by the Tzanck smear and pathology. The confirmation of the causative agent is obtained through viral culture, which is the gold-standard method, or by polymerase chain reaction (PCR). Serologic tests have high sensitivity and specificity, but have limited usefulness because of the high prevalence of the virus.

Differential Diagnosis

The orolabial lesions of the primary infection should be differentiated from aphthous stomatitis, pemphigus vulgaris, erythema multiforme, Stevens–Johnson syndrome, herpangina, and hand-foot-and-mouth disease. Lesions only involving the face and lips should also be differentiated from impetigo.

Genital herpes should be mainly differentiated from other STDs, such as syphilitic chancre, chancroid, or lymphogranuloma venereum. Other conditions to bear in mind are erosive lichen planus, lichen sclerosus, atopic dermatitis, and urethritis.

Therapeutic Approach

An overall evaluation of the clinical signs, symptoms, and general health of the patient is essential to the success of therapeutic interventions for HSV infection. Other factors influencing treatment selection include the site of infection and the primary or recurrence status. The current management approach to HSV infection does not target viral eradication, but rather the prevention of transmission, suppression of recurrence, attenuation of clinical course, viral shedding, and complications, as well as palliation and promotion of healing [3].

Antivirals used in the primary infection and recurrent genital or orolabial episodes are the same, with the route of administration and the treatment time determined by the severity of the disease and the patient's condition. In primary and recurrent uncomplicated infections, the most effective treatment is oral antivirals [6]. When used early, preferably within 48 h of onset (higher viral replication period), the duration of symptoms and potential transmission are reduced [3, 7]. Acyclovir is the oldest antiviral used, but its short half-life requires it be taken several times a day. Famciclovir and valacyclovir have a longer half-life and allow fewer doses per day, which may offset their higher costs and ensure adherence to treatment [8]. Therapeutic options and dosages of the main antivirals for the treatment of HSV are summarized in Table 10.2.

Treatment with topical medications, namely acyclovir 5% and penciclovir 1%, may be used in minor recurrent episodes. However, this route is less effective than systemic treatments for not reaching viral replication sites beyond the visible lesions [3, 5, 8].

Relief measures for local symptoms can be used, such as topical anesthetics. Ingestion of cold food and cold compresses are also valid, as well as the use of topical antiseptics to minimize the risk of bacterial infection.

Chronic suppressive therapy is indicated for patients with genital or orolabial herpes who present six or more episodes per year. This reduces the risk of transmission of infection and improves quality of life. The same medications used in the episodes are used indefinitely in continuous regimens, ranging from 4 to 12 months in studies already conducted [4, 7, 8].

New drugs under study attempt to reduce the severity of the attacks and the risk of transmitting the virus. A recently published study suggested an efficacy of approximately 51% for

Table 10.2 Treatment of herpes simplex

Primary infection in immunocompetent patients	Acyclovir 200 mg 5×/day or 400 mg 3× or 5×/day for 7–10 days
	Children: 15 mg/kg
	Valacyclovir 500–1,000 mg/day for 7 days
	Famciclovir 250 mg tid for 7–10 days
Recurrence in immunocompetent patients	Acyclovir 400 mg tid or 200 mg 5×/day for 5–10 days or 800 mg tid for 2 days
	Valacyclovir 500 mg bid for 3 days or 1 g/day for 5 days or 2 g bid for 1 day
	Famciclovir 125 mg bid for 5 days or 1 g bid for 1 day or 1500 mg 1× in 1 day
Infection in immunocompromised patients	Acyclovir 400 mg tid or 200 mg 5×/day or 5–10 mg/kg IV 8/8 h until lesions improve
	Valacyclovir 500–1000 mg bid until lesions improve
	Famciclovir 500 mg bid until lesions improve
Chronic suppression	Acyclovir 400 mg bid
	Valacyclovir 500–1000 mg/day
	Famciclovir 250 mg bid
Eczema herpeticum	Acyclovir 15 mg/kg (maximum 400 mg) 3–5×/day for 7–14 days. Consider IV if generalized
	Valacyclovir 1 g bid 7–14 days
	Famciclovir 500 mg bid 7–14 days

Dosage for oral use, unless IV use is stated
bid twice daily, *IV* intravenously, *tid* three times a day

tenofovir gel topically applied before intercourse to reduce transmission of HSV-2 in South African women [9].

Pritelivir is a new drug that inhibits viral replication by inhibiting the helicase-primase enzyme, which does not require activation by phosphorylation. A recent study of 156 participants showed superiority over the placebo in reducing viral replication and the number of days with lesions in patients with a history of recurrent genital herpes without comorbidities, with better results at a dose of 75 mg/day [10].

Intravenous acyclovir is indicated for severe disease or immunocompromised patients (10–20 mg/kg thrice daily for 7–14 days). Acyclovir resistance may occur mainly in immunocompromised patients, requiring treatment with intravenous drugs such as foscarnet (40 mg/kg intravenously (IV) every 8–12 h for 14–21 days) and cidofovir (5 mg/kg/week IV for 2 weeks an afterward, every other week). Both medications are nephrotoxic, requiring hydration and monitoring of renal function [2–4].

There is currently no licensed vaccine available for HSV. The development of vaccines capable of preventing infection by HSV-1 and -2 remains a challenge [6, 11]. The vaccine models tested thus far have not achieved the same results obtained in laboratory animals and have not reached phase II clinical studies [11].

Varicella Zoster Virus (HHV-3 or VZV)

Introduction
Varicella zoster virus (VZV) is the cause of two diseases, varicella and herpes zoster, also popularly known as chickenpox and shingles, respectively. Varicella is highly contagious and affects a younger age group, with predominance in children under 10 years of age. Herpes zoster, which is the result of viral reactivation, affects more adults and elderly after the sixth decade of life, with a greater frame of morbidity [2, 12].

Epidemiology
VZV is present throughout the world. United States data show that more than 95% of its population is seropositive for this virus. Some differences are noteworthy in relation to varicella and herpes zoster.

Varicella occurs predominantly in children under 10 years of age, reaching 90% of cases in this age group. The risk of acquiring the disease is higher the closer the contact with the infected individual. The disease has a peak incidence in winter and spring in populations of temperate climates, with epidemics occurring every 2–5 years [2, 13]. Before the introduction of the vaccine against the virus, global rates were estimated at 4 million cases per year including all age groups. These numbers decreased drastically after the

start of the administration of the vaccine, which was validated in the United States in 1995, with a decrease of 97% in incidence between 1995 and 2010. The most severe forms usually occur in people older than 12 years of age, immunocompromised patients or those with immune deficiencies, fetal exposure between 8 and 26 weeks of gestation, and fetal exposure to maternal infection from 5 days before to 2 days after birth [13].

Etiopathogenesis

VZV is an enveloped neurotropic virus with double-stranded DNA, and belongs to the Herpesviridae family and the Alphaherpesvirinae subfamily, with humans as the specific reservoir, although some mammals may carry the latent virus [12].

Varicella is highly contagious, transmitted through contact with infected people who expel the virus through the respiratory route (droplets). Transmission may also occur through direct contact with the secretions of the skin lesions, the transplacental route, during a blood transfusion or contact with people with herpes zoster. Transmission starts 1–2 days before the onset of a rash and continues until all lesions are at the crust stage. The incubation period can range from 10 to 21 days. After contact, through an inhalation route, infection occurs in the respiratory mucosa and replication in the regional lymph nodes, and the virus is transported to the liver and spleen, which constitutes the first viremia. During the second viremia, the virus is transported via capillary endothelial cells to the skin and mucous membranes, and subsequently migrates into dorsal root ganglion cells. The virus can remain latent after infection or after the vaccination [2, 12, 13].

Herpes zoster has the characteristic of being significantly less contagious than varicella, transmission occurring by direct contact with the fluids of cutaneous lesions. The virus is neurotropic and can maintain latency for long periods. The major sites where the virus lodges are the ganglia of the cranial nerves, dorsal root ganglia, and autonomic ganglia of the neuraxis. In addition to the risk factors mentioned above, herpes zoster can be triggered by stress, trauma, immunosuppression, or fever [12].

Clinical Presentation

Varicella presents prodrome of fever, malaise, headache, and abdominal pain 1–2 days before the onset of a vesicular rash. The fever lasts around 3–5 days. Lesions begin on the face and scalp, evolving into the trunk and extremities, and can affect the mucous membranes, such as the oropharynx, conjunctiva, and genital region. Initially the lesions are erythematous and pruritic maculopapular rashes, after which vesicles of clear serous content and an erythematous halo appear; in the terminal stage crusts are formed, which after healing can progress to scars (Fig. 10.5a–d). Crusts can last up to 2 weeks before total disappearance. Characteristically the patient has skin lesions at various stages of evolution, since new lesions may appear up to 7 days after the onset of the infection. Usually 250–500 vesicles are observed, which may surpass 1000. In healthy children the infection is benign and self-limited, evolving to curability within 7–10 days [2].

In adults and immunocompromised patients, the infection can show a longer period of fever, a greater number of lesions, longer duration, and increased risk of secondary infection.

Congenital infection is more serious if the mother is affected in the first trimester of pregnancy. The risks to the fetus include skin scars, hypoplasia of limbs, neurological disorders (cortical atrophy and psychomotor retardation), and ocular changes [13, 14].

The most common complication of cutaneous lesions is secondary bacterial infection associated with Gram-positive organisms. Varicella-associated pneumonia is most common in adults and immunocompromised patients. The involvement of the CNS, although rare, may occur, manifesting as cerebellar ataxia, encephalitis, and Reye's syndrome. Other rare complications include purpura, thrombocytopenia, ischemic stroke, cerebral venous thrombosis, transverse myelitis, Guillain–Barré syndrome, premature birth, and ocular changes (unilateral anterior uveitis, corneal lesion, optic neuritis, acute retinal necrosis, and necrotizing scleritis) [2, 13].

Herpes zoster, consisting of the reactivation of latent varicella infection, most often begins with

Fig. 10.5 (**a–d**) Varicella: cutaneous and oral lesions

neuralgia prodromes (severe pain, itching, tingling) that precede the appearance of skin lesions at 1–5 days. The lesions are characterized by grouped vesicles on an erythematous base, following the distribution of a dermatome, usually without crossing the midline (Fig. 10.6a, b). Rare cases manifest as pain without cutaneous lesions, known as "zoster sine herpete" (i.e., zoster without cutaneous eruption). Lesions present remission in 2–4 weeks and most patients do not assume significant systemic symptoms [14].

The most affected areas are the chest, skull (especially the trigeminal nerve), lower back, and cervical region. Ocular involvement should be suspected, given the risk of blindness. Lesions in the nasal wing may suggest eye involvement even before the emergence of lesions around the eyes. Ophthalmic herpes zoster normally presents with vesicles on an erythematous base in the periorbital region, eyelid edema, and conjunctival edema. Eye pain or blurred vision may indicate retina necrosis. Evaluation by an ophthalmologist is indicated when there is suspicion of ocular involvement. When reactivation occurs in the geniculate ganglion, it is called Ramsay–Hunt syndrome and is characterized by lesions in the ear canal, tongue, and/or hard palate, and facial nerve paralysis may occur. Neurologic involvement may be manifested by altered mental state, headache, focal deficit, paresis, muscle weakness, ataxia, and tremors, which may correspond to vasculopathy, myelopathy, radiculopathy, or cerebellitis [12].

Fig. 10.6 (**a**, **b**) Herpes zoster

Other complications of herpes zoster can occur at the site of eruption, such as bacterial superinfections by *Staphylococcus aureus* and *Streptococcus pyogenes*, hyperpigmentation, and evolution of cutaneous scar, besides postherpetic neuralgia, which will be mentioned later.

Diagnosis and Complementary Examinations

The diagnosis of varicella and herpes zoster is clinical, based on history and physical examination, which shows the characteristics of the lesions and their distribution. Diagnostic confirmation may require other methods, including serology, viral culture, direct immunofluorescence staining, indirect immunofluorescence, PCR, and Tzanck smear performed with material collected from the fluid of the vesicles, crusting lesions, skin or oropharynx swab, cerebrospinal fluid, tissue samples, saliva, or blood. For faster results the Tzanck smear and direct immunofluorescence staining is used. The Tzanck smear reveals giant multinucleated epithelial cells, which does not differentiate between infection by the VZV and herpes simplex. Direct immunofluorescence staining differentiates the infection of HSV from VZV and is more sensitive than cultures, but less so than PCR. PCR is the most suitable approach because of its high sensitivity and specificity. The culture is the most specific, although it takes about a week for the result, which makes it unfeasible to plan the antiviral therapy [2, 12, 14].

Differential Diagnosis

The differential diagnosis of varicella includes vesicular rash caused by enterovirus or *S. aureus*, herpes simplex, insect bites, erythema multiforme, scabies, papular urticaria, drug eruption, contact dermatitis, herpetiformis dermatitis, Stevens–Johnson syndrome, guttate psoriasis, pityriasis lichenoid, syphilis, smallpox, and congenital histiocytosis.

Herpes zoster should be differentiated from HSV, smallpox, contact dermatitis, impetigo, cellulitis, bites and stings, candidiasis, autoimmune bullous disease, dermatitis herpetiformis, drug reactions, and Sweet's syndrome.

Therapeutic Approach

Varicella in immunocompetent children can be treated symptomatically with antipyretics (e.g., acetaminophen), antihistamines, calamine lotion, and tepid baths [2].

The use of acyclovir in chickenpox is approved by the FDA for children over 2 years of age and for adults because of its potential to reduce the time of infection and severity. Ideally it should be started within 24 h of onset of cutaneous lesions, with a margin of up to 72 h. In adults, because of the higher risk of severity, treatment with antiviral drugs is always recommended. In children 2–16 years of age, 20 mg/kg four times a day for 5 days is utilized, with a maximum of 800 mg/day [2, 3]. In persons over 16 years of age, 800 mg five times a day for 5 days is recommended [2, 12, 13].

In herpes zoster lesions, one can make use of aluminum or Burow acetate solution. For the pain one can use the same medications as for varicella, but often, because of its greater intensity, medications such as opioids and tramadol may be included. Opioid options for moderate to severe pain include codeine, hydrocodone, oxycodone, methadone, and morphine. The use of acyclovir, as well as in varicella, reduces the duration, severity of the infection, and pain, but there is no evidence that it can prevent postherpetic neuralgia [15]. It is indicated to be started within 72 h, but it is accepted that its introduction can occur within the first week. Formal indications for the use of acyclovir include immunocompetent adults older than 50 years with moderate to severe symptoms, ophthalmic herpes zoster, disseminated herpes zoster, and immunocompromised patients. Antiviral and available doses are summarized in Table 10.3. In cases of severe disease, CNS involvement, disseminated varicella zoster, or herpes zoster in immunocompromised patients, intravenous acyclovir is indicated. In children under 12 years of age the acyclovir dose is increased to 20 mg/kg. In cases of resistance to acyclovir, the patient will benefit from the use of foscarnet 40 mg/kg intravenously every 8 h for 10 days. Approved in some countries, brivudine 125 mg orally, once daily for 7 days, is another option. In cases of eye or hearing impairment, the ophthalmologist and otolaryngologist should be consulted. For herpes zoster with involvement of the retina, intravenous acyclovir is preferred over oral administration [2, 13].

Prevention

Vaccine: For the prevention of the disease and severe forms, the Advisory Committee on Immunization Practices (ACIP) recommends two doses of the live attenuated Oka varicella zoster virus vaccine, with seroconversion rates of up to 96% in healthy children [16]. The first dose should be administered between 12 and 15 months of age and the second between 4 and 6 years of age. The second dose of vaccine may be combined with the measles, mumps, and rubella (MMR), forming the MMRV. In children under 13 years of age, the second dose of vaccine should be administered within a range of 3 months or more from the first dose. In persons older than 13 years, doses should be spaced 4–8 weeks apart. ACIP emphasizes the importance of the vaccine in special situations, such as health professionals, carers of immunocompromised people, teachers, carers of children, college students, institutionalized patients or employees of these institutions, military personnel, and international travelers [16]. The vaccine is contraindicated in pregnant women, blood dyscrasias, leukemia, lymphoma, malignant neoplasm of the bone marrow or lymphatic system, use of drugs at immunosuppressant doses, severe disease carriers, history of anaphylaxis or anaphylactoid reaction to gelatin, neomycin, or other components of the vaccine, and history of having received red blood cells, plasma, or immunoglobulin in the last 3–11 months [17]. Postexposure prophylaxis should be carried out with the vaccine in indi-

Table 10.3 Treatment of varicella and herpes zoster

Age group	Disease	Antiviral dose
2–16 years	Varicella	Acyclovir 20 mg/kg po 4×/day × 5 days (maximum: 800 mg/day)
<12 years	Herpes zoster	Acyclovir 20 mg/kg IV q8 h × 7–10 days
>16 years	Varicella and herpes zoster	Acyclovir 800 mg po 5×/day × 7 days
		Valacyclovir 1 g po tid × 7 days
		Famciclovir 500 mg po tid × 7 days
		Acyclovir 10 mg/kg IV q8 h × 7–10 days
		Foscarnet 40 mg/kg IV q8 h × 10 days
		Brivudine 125 mg po qd × 7 days

Recommended dose of antivirals based on disease and age group [2, 3]
IV intravenously, *po* orally, *q8 h* every 8 h, *qd* once a day, *tid* three times a day

viduals who show no evidence of immunity and in susceptible patients, and ideally up to 3–5 days after exposure to prevent disease or severe forms [18].

The vaccine for herpes zoster was developed for the prophylaxis of herpes zoster and showed a 50% reduction in the incidence of the disease in the treated group compared with the control group. It is recommended for adults older than 60 years [19]. The FDA had approved it for adults aged 50 through 59 years but the ACIP declined to recommend the vaccine for this age group because of short-term vaccine efficacy. Contraindications to vaccine for herpes zoster include immunosuppression (e.g., HIV infection with CD4 lower than 200/mm^3, hematologic or lymphatic malignancies, and using immunosuppressive therapy), acute herpes zoster infection, or other active severe acute disease [19, 20].

Varicella zoster immune globulin: The varicella zoster immune globulin (VZIG), which is prophylactic through passive antibodies, provides temporary passive immunity. It should be administered 96 h after exposure and lasts 3 weeks. It is indicated as prophylaxis in immunocompromised patients or pregnant women without evidence of immunity to varicella zoster, newborns of mothers who had chickenpox 2 days before to 5 days after birth, premature newborns of 28 weeks or more who were exposed to varicella during the neonatal period with mothers without evidence of immunity, and preterm infants of less than 28 weeks or weighing less than 1000 mg that were exposed during the neonatal period [2, 12, 13]. Immune globulin is administered as a single intramuscular dose, according to Table 10.4.

Table 10.4 Varicella zoster immune globulin

Weight	Dose
Below 2 kg	62.5 IU
2.1–10 kg	125 IU
Above 10 kg	625 IU

Single intramuscular dose

Postherpetic Neuralgia

Postherpetic neuralgia (PHN) is the most common complication of herpes zoster, and is defined as pain that persists for more than 3 months after the resolution of cutaneous lesions. The incidence is estimated at 9–34%, and the risk is higher in the elderly and in persons with shingles with severe acute pain, exacerbated cutaneous eruptions, ophthalmic herpes, and intense prodromal pain. Generally pain is resistant to commonly used pain relievers, so some alternative medications become necessary [21]. Therapeutic options for PHN are listed in Table 10.5.

Epstein–Barr Virus (HHV-4)

Epidemiology

Epstein–Barr virus (EBV) is also known as human herpes virus type 4 (HHV-4) of the Gammaherpesviridae family.

EBV has a worldwide distribution and high epidemiological prevalence, with about 95% of infected adults around the world, and in developing countries transmission occurs almost universally in childhood [22–24].

EBV is transmitted primarily by the saliva of infected individuals, and hence the infectious mononucleosis (IM) is also called "kissing disease." The virus is secreted by saliva in high concentrations for longer than 6 months after primary infection. The infection tends to be mild and with nonspecific symptoms in children under 4 years of age, while the characteristic clinical presentation of IM occurs mainly in adolescents and young adults [22, 24]. Sexual transmission does not seem to play an important role. Human beings are the only natural reservoir of the virus [2, 22].

Etiopathogenesis

After inoculation of EBV via infected saliva, the virus infects mucosal epithelial cells of the oropharynx and B lymphocytes (connection with the CD21 receptor), where it initiates replication [2, 22]. The virus still has the capacity to infect other leukocytes, such as T cells and natural

Table 10.5 Treatment of postherpetic neuralgia

Medications	Observation
Amitriptyline 10 mg/day (initial) to 50–100 mg/day	Tricyclic antidepressants are effective in treating chronic pain. They should be started at low doses. A baseline ECG is required
Nortriptyline 10–25 mg/day (initial) to 30–75 mg/day	
Desipramine 10–25 mg/day (initial) to 50–150 mg/day	
Venlafaxine and duloxetine	Serotonin reuptake and noradrenaline are effective in treating chronic pain
Pregabalin 150–300 mg/day up to 600 mg/day	Anticonvulsant with good patient acceptance
Gabapentin up to 1800 mg/day divided into 3 doses daily	
Carbamazepine and valproic acid	Anticonvulsants with less patient acceptance
Opioids	Good option, requiring concomitant prophylaxis for constipation
Tramadol	Cholinergic syndrome risk if administered concurrently with serotonin reuptake inhibitors or tricyclic antidepressants
5% topical lidocaine	Has low systemic absorption and significantly reduces pain and allodynia
Capsaicin	After repeated application on site, causes depletion of substance P and other neuropeptides of the nociceptive fibers, which causes analgesia
	Owing to the possibility of local irritation and stinging, its use is indicated after treatment with lidocaine
Other treatments	Observation
Epidural blocks, intrathecal injection, and sympathectomy	Have not shown favorable cost-benefit because of adverse effects presented
Spinal cord stimulation	Encouraging results in intractable pain and the incidence of postherpetic neuralgia
Botulinum toxin	Reduction in pain and improved quality of sleep, lasting about 3–4 months

killer (NK) cells, as well as endothelial and smooth muscle cells. After an incubation period of about 30–50 days, symptoms due to high viremia occur: pharyngitis, fever, and lymphadenopathy, which characterize the infectious mononucleosis picture, albeit less severe [2, 23, 24]. After resolution, some B cells become infected and the latency of the virus is established throughout the life of the individual. Immunocompetent patients, through preserved cellular immune response, can prevent the replication of the virus in the infected cells according to the actual status of latency. Especially in immunocompromised patients, failure to control the replication of cells chronically infected with the virus results in these cells continuing to express their proteins, leading to the risk of lymphoproliferative disorders related to infec-

tion. Reactivation of latent virus present in infected lymphocytes in the oropharynx may occur, causing viral excretion during the entire life of the host [2, 23].

Clinical Manifestations

Infectious mononucleosis is the manifestation of primary EBV infection in about 30–50% of those infected, and occurs most commonly in adolescents and young adults between the ages of 15 and 25 years [2, 24].

The incubation period in adolescents and adults lasts approximately 30–50 days, after which the characteristic triad of fever, pharyngitis, and lymphadenopathy (especially cervical) is seen in >80% of patients. Common accompanying symptoms include malaise, fatigue, chills, and headache. Fever can last up to 10 days. Splenomegaly

is found in >50% of patients and can be accompanied by hepatomegaly. Other clinical findings may include exudative pharyngitis (often gray–white), anorexia, nausea, vomiting, cough, and arthralgia. Symptoms usually improve in about 2–4 weeks, while lymphadenopathy may last up to 6 months.

The cutaneous manifestation associated with IM is a morbilliform eruption (in approximately 3–15% of cases) on the trunk and upper extremities, which may spread to involve the face and forearms, typically lasting up to 7 days [25]. The occurrence of a maculopapular rash, which occurs 7–10 days after administration of antibiotics (prescribed, in most cases, for the treatment of symptoms of IM that are associated with streptococcal pharyngitis) is very characteristic of IM (Fig. 10.7a–c). It was first observed with the use of ampicillin (occurring in up to 95% of cases), but can occur with various other antibiotics. The rash lasts about 1 week. Hemolytic anemia and thrombocytopenia with associated thrombocytopenic purpura and disseminated intravascular coagulation can occur. Neurologic complications are rare (Guillain–Barré syndrome, facial palsy, aseptic meningitis, and encephalitis) [24].

Other manifestations resulting from infection with EBV related to acute or chronic infection/viral reactivation are:

- Lipschütz ulcers: Acute genital ulcers not related to sexual transmission. They occur as a complication of acute infection in adolescents or prepubescent girls, are usually located in the region of the labia minora, and are painful. They have important differentiation with STDs and suspected sexual abuse [22].
- Oral hairy leukoplakia: Benign change related to immunosuppression, indicative of disease progression to AIDS in HIV-positive individuals. White or gray plaques, firmly adhered to the mucosa of the dorsal or lateral side of the tongue, are characteristic. They are mostly asymptomatic.

- Gianotti–Crosti syndrome: EBV has increased in incidence as a result of this disorder (see Gianotti–Crosti syndrome in this chapter).
- Other skin manifestations related to EBV are hydroa vacciniforme, erythema multiforme, erythema nodosum, erythema annulare centrifugum, pityriasis lichenoides, drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, and vasculitis purpura, among others [22, 23].
- Neoplastic diseases associated with EBV are oropharynx carcinoma, B- and T-cell lymphomas, NK cell lymphoma, Burkitt's lymphoma (especially the African endemic form), Hodgkin's lymphoma, and hemophagocytic syndrome. The causal relationship between the EBV and cutaneous T-cell lymphomas is still controversial [26, 27].

Diagnostic and Complementary Examinations

Clinical and laboratory data are important for IM diagnosis (see Box 10.1).

Leukocytosis with the presence of atypical lymphocytes (20–40%), thrombocytopenia, and lightly to moderately elevated transaminases may occur in IM in 50% of patients.

Heterophile antibody titers >1:40 are considered positive for IM. The most widely used method for detecting heterophile antibodies is the qualitative rapid slide test, known as the mono-

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Box 10.1 Laboratory Diagnosis Key points

EBV infection

Up to 10% of patients with IM are heterophile negative

For suspected primary EBV infection, a heterophile antibody test should be performed, followed by EBV serology when the heterophile test is negative, but clinical suspicion remains high

EBV-encoded RNA in situ hybridization is considered the gold standard for detecting and locating latent EBV in tissue samples

Fig. 10.7 (**a–c**) Amoxicillin-induced maculopapular rash in a child with IM caused by EBV

spot test, a latex agglutination assay, which has reported sensitivity of 85% and specificity approaching 100%.

Despite high sensitivity and specificity, the heterophile antibody tests have several limitations. The test has a significant false-negative rate during the first week of infection, and is of limited use in children under 4 years of age. False-positive results have been reported in some diseases, such as malaria, rubella, and primary HIV infection.

Acute EBV infection is uniformly characterized by a rapid IgM and IgG antibody response to the viral capsid antigen (VCA). Anti-VCA IgM is the single most valuable and specific serologic test in confirming primary EBV infection. The response appears before the onset of symptoms and remains positive for up to 3 months. IgG-VCA peaks later in the acute phase, declines over several weeks to months, and then remains positive for life [22].

Differential Diagnosis

IM must be differentiated from other viral infections that present skin rash, lymphadenopathy, and pharyngitis, such as streptococcal infection, CMV, toxoplasmosis, HHV-6, acute viral hepatitis, and acute retroviral syndrome from HIV, which require a combination of clinical and laboratory examinations for diagnosis [24, 25].

Therapeutic Approach

Only supportive treatment is needed for most patients suffering from IM, with medication to control the symptoms, proper hydration, and nutrition. Relative rest is recommended, but without the necessity of restriction to bed rest. Acyclovir did not show a reduction of viral replication or a significant alteration to the course of infection [24].

One study showed that valacyclovir used for 1 year in chronically infected patients with EBV reduced the frequency of infected B lymphocytes detected in the peripheral blood in comparison with controls without treatment. The authors estimated that it would take 11 years of daily treatment to cure the infection in an individual [8].

The use of corticosteroids is reserved for complicated cases of IM, such as the obstruction of the upper airways, hemolytic anemia, and thrombocytopenia due to its adverse effects. However, in both complicated cases and cases without gravity, studies with the highest level of evidence based on its use are lacking. Associated lymphoproliferative disorders can achieve resolution with an improvement in immunosuppression, common in these cases, or the need for associated chemotherapy [2, 24].

Cytomegalovirus (HHV-5)

Epidemiology

Also known as human herpes virus type 5 (HHV-5), cytomegalovirus (CMV) is an endemic DNA virus worldwide. The infection is inversely related to socioeconomic status, approaching up to 100% in low-income countries and about 60–70% in developed countries [2, 28]. The risk of acquisition of the infection is higher in childhood (especially children who attend daycare centers) and in adolescence, as well as during a period of sexual

activity. CMV transmission by blood transfusion may occur in about 3% of transfused blood units, owing to the presence of infected leukocytes [2].

The prevalence of clinically evident infections has increased with the growing phenomenon of immunodepression (such as in HIV infections, organ transplants, immunosuppressive treatments), representing an important cause of morbidity and mortality in these populations. Congenital infection occurs in about 0.5–2% of gestations [29].

Etiology

CMV is transmitted by saliva, blood, urine, breast milk, semen and cervicovaginal fluids, solid organs, or transplanted stem cells. Vertical transmission is more probable during a primary infection of the mother (about 40%, versus <1% of infection in the case of recurrent infection), which occurs principally by transplacental transmission, early in gestation [2]. After the infection it enters an incubation period of 4–8 weeks and spreads through the body by leukocyte infection. It displays tropism for various cells (endothelial, epithelial, smooth muscle, macrophages, and neuronal). The virus becomes latent and temporary reactivations may occur, asymptomatic in most cases, with viral shedding in the urine or saliva, enabling the transmission of CMV. Cellular immunity, primarily mediated by $CD8^+$ T cells, presents a major role in the immune control of the infection. In weak immune conditions, persistent viral replication leads to sustained viremia and viral dissemination to various organs, causing cellular damage and an inflammatory response that causes clinical manifestations.

Reinfection can also occur by another antigenic type of CMV with features similar to viral reactivation. In immunocompetent children and adults the most frequently infected organs are lymphoid tissues, while in immunocompromised patients the retina, lungs, liver, and gastrointestinal tract can be affected. Congenital and neonatal infection commonly involves the nervous system [2, 29].

Clinical Manifestations

Clinical presentation varies widely among immunocompetent and immunocompromised patients. In immunocompetent patients, in about 90% of

cases an acute infection is asymptomatic, and when symptomatic is manifested as a syndrome similar to mononucleosis by EBV, with fever, myalgia, nonexudative pharyngitis, lymphadenopathies as well as morbilliform skin rash, urticaria, or purpura [29]. Hepatosplenomegaly may occur.

A skin rash, similar to the occurrence in EBV infection, may appear after the use of ampicillin or other antibiotics in approximately 80–100% of cases. A similar picture is also observed after blood transfusion with CMV-contaminated blood.

The infection is self-limiting, and usually benign, with only rare occurrence of complications such as fulminant hepatitis, Guillain–Barré syndrome, encephalitis, meningitis, retinitis, myocarditis, pneumonia, gastrointestinal disorders, and hematologic abnormalities (hemolytic anemia and pancytopenia).

When there is impairment of cellular immunity, replication and persistent viral dissemination occur, causing lesions in the primary infection and, principally, in reactivation/recurrence of the infection.

The main manifestations in HIV patients occur at CD4 levels below 100, and consist of chorioretinitis, esophageal ulcers, colitis, pneumonitis, and adrenal and CNS involvement. Mortality can be high (up to 80%). In transplant patients, viral reactivation by the required posttransplant immunosuppression or infection acquired from infected donor organ to a seronegative receiver may occur.

The most prevalent and more severe manifestations are that of the gastrointestinal tract and interstitial pneumonitis.

Congenital CMV infection may be asymptomatic at birth, with only 10% of infants manifesting symptoms such as jaundice, hepatosplenomegaly, cardiovascular and gastrointestinal abnormalities, chorioretinitis, and intracranial calcifications, constituting the so-called cytomegalic inclusion disease. Many asymptomatic cases at birth may present posterior sequelae, being one of the major infectious causes of sensorineural deafness and mental retardation. Cutaneous manifestations may or may not be specific to the infection, the former being more related to immunosuppression. Nonspecific is a rash of the acute infection (described above) and lesions of the CMV inclusion disease, such as petechiae, purpura, jaundice, and papular-nodular lesions related to hemopoiesis in the dermis ("blueberry muffin" lesions). The lesions specific to cytomegalovirus, most common in immunocompromised patients, are ulcerations, especially in the anogenital region and thighs. Nodular disseminated cutaneous lesions, warty morbilliform urticaria, and bullae are also described as being related to CMV.

Many of these lesions are associated with HSV infection, especially in HIV-positive patients [30], and studies in the literature question the actual role of CMV in many cutaneous lesions found [31].

Diagnostic and Complementary Examinations

The diagnosis is made by clinical suspicion and confirmation of etiology through laboratory tests. Laboratory alterations such as lymphocytosis, thrombocytopenia, and elevated liver transaminases may occur. CMV culture, performed on human fibroblasts, conducted by collecting lesion material of affected organs or blood, urine, cerebrospinal fluid, semen, or cervicovaginal fluid, is considered the gold standard but is time consuming, requiring at least 2 weeks for results. In lesions of the oral cavity, the test may not be specific because of the possible excretion of the virus from other regions of the upper gastrointestinal tract.

Histopathology is of great value, and shows the cytopathic changes in CMV upon hematoxylin–eosin (HE) staining as extended endothelial cells with characteristic intranuclear inclusions ("owl eyes") considered pathognomonic of infection [2]. Although specific, this finding has lower sensitivity than the culture. Electron microscopy shows no ability to differentiate from other herpesviruses.

PCR is very specific and fast, but does not distinguish primary infection from reactivation.

Specific serologic tests can help distinguish between recent infection or reactivation, the former by detection of IgM and IgG antibodies in high titers and the latter by detection of only IgG. Serology is also useful in the evaluation of congenital infection by the presence of IgM antibodies in newborns [29].

Differential Diagnosis

The differential diagnosis is made with IM by EBV, acute toxoplasmosis, acute viral hepatitis, acute retroviral syndrome by HIV, and DRESS syndrome in acute infections. Ulcerous cutaneous lesions should be differentiated from HSV. Since several atypical cutaneous manifestations may occur, CMV must always be considered in dermatologic disseminated disease in immunocompromised patients.

Therapeutic Approach

Prevention and Treatment

Since CMV is a benign, self-limiting disease, immunocompetent patients generally do not require treatment, only supportive care.

Treatment in immunosuppressed patients consists of pre- and posttransplant antiviral prophylaxis in those susceptible to infection, and antiviral treatment in patients with manifestations of the active disease. The drugs used are intravenous ganciclovir and oral valganciclovir for about 14–21 days. In the congenital infection, the same drugs are also used in symptomatic neonates for 6 weeks [2, 28]. A recent study showed moderate benefit from the use of valganciclovir for 6 months for hearing loss outcomes and neurologic changes compared with 6 weeks of treatment [32]. Resistant infections to ganciclovir and valganciclovir can be treated with foscarnet or cidofovir. Anti-CMV immunoglobulin can be used in more severe cases for prophylaxis or treatment, in combination with antiviral agents.

Several experimental CMV vaccines have advanced to clinical evaluation. The aim of CMV vaccine is disease prevention in congenital infection and post-transplant disease.

Human Herpesvirus 6 (HHV-6)/ Exanthema Subitum

Synonyms: Roseola infantum, sixth disease

Introduction

Human herpesvirus 6 (HHV-6) has two variants, A and B, although new evidence suggests that these subtypes are distinct viruses, each with its own strains. HHV-6A has been found more commonly in skin biopsy specimens from immunocompromised patients and is considered a possible cofactor in AIDS progression. In comparison, HHV-6B is thought to be the primary etiologic agent in exanthema subitum, also known as roseola infantum or sixth disease [33].

Epidemiology

HHV-6A and HHV-6B are ubiquitous viruses that are detected in human populations worldwide. Current serologic assays do not permit discrimination of HHV-6A and HHV-6B infections [34]. HHV-6 infection is usually acquired very early in life, between 6 months and 2 years of age, following the loss of protective maternal antibodies. At an even earlier period of life, congenital infection following intrauterine transmission has been reported in about 1% of children. Around 21% of patients present the typical clinical picture of exanthema subitum in the primary infection, while in approximately 20% of cases the disease is asymptomatic. Data from the adult population in developed countries have shown that infection in this age group exceeds 90% [34].

Etiopathogenesis

HHV-6 is a double-stranded DNA virus, of the Roseolovirus genus and a member of the Betaherpesviridae subfamily (see Box 10.2) [35].

> **Box 10.2 Roseolovirus**
> The Roseolovirus genus of the Betaherpesvirus subfamily is composed of three enveloped, double-stranded DNA viruses: HHV-6A, HHV-6B, and HHV-7.

Transmission occurs via the oral route, purportedly by saliva. The incubation period may vary between 10 and 15 days. The virus replicates in the salivary glands and satellite lymphoid tissues of the oropharynx, probably the tonsils and cervical lymph nodes. Systemic diffusion of infection would then occur by the blood route. This spread leads to the active, abortive, or latent infection of susceptible cells in other organs, including T lymphocytes and monocytic cells in lymphoid tissue and the liver, kidney, and skin epithelial cells, hematopoietic stem cells in bone marrow, and neuroglial cells in the CNS [34].

After primary HHV-6 infection, the virus establishes lifelong latency in CD4+ T lymphocytes, with the potential for reactivation. Immunosuppressed patients are at particular risk for HHV-6 reactivation, sometimes with severe consequences.

Recent studies have shown that HHV-6 has the unique ability to integrate into chromosomal telomeres of infected cells. When this occurs in a germ cell, vertical transmission of inherited chromosomally integrated (ci)HHV-6 results in offspring with latent HHV-6 DNA in every nucleated cell of the body. Studies have shown that 0.2–3% of the study population harbors the entire genome of HHV-6A and HHV-6B integrated at different chromosomal locations. There is evidence that biologically active HHV-6 can reactivate in individuals with inherited HHV-6 and cause disease [34].

Clinical Presentation

Exanthema subitum is the disease caused by HHV-6 during the primary symptomatic infection. The classical clinical picture is of an infant with a high fever (38.9–40.6 °C) that lasts for 3–5 days, followed by a characteristic rash on defervescence. The fever may be intermittent and tends to peak in the early evening. The cutaneous eruption usually lasts for 24–48 h and may develop before the temperature returns to normal or up to 2 days afterwards. The lesions are discrete, circular, or elliptical "rose-red" macules and papules that are 2–5 mm in diameter and occasionally surrounded by a white halo. The cutaneous eruption commonly affects the trunk, proximal extremities, neck, and less often the face. An enanthem of red papules on the soft palate (Nagayama's spots) may also be seen, and

ulcers on the uvula and at the palatoglossal junction represent a characteristic finding. Eyelid edema, mild upper respiratory symptoms, injection of the tympanic membranes, cervical or occipital lymphadenopathy, and a bulging anterior fontanelle may also be evident [2].

Serious complications are rare, although there are reported cases of hepatitis, thrombocytopenia, mononucleosis-like syndrome, colitis, gastroenteritis, myocarditis, febrile seizures, meningoencephalitis, and encephalitis [33, 34].

It has been hypothesized that HHV-6, as well as HHV-7, has a role in the pathogenesis of pityriasis rosea and DRESS syndrome, as well as other conditions such as Stevens–Johnson syndrome, thrombocytopenic purpura, purpura fulminans, gloves and socks syndrome, scleroderma, and Gianotti–Crosti syndrome [33].

Diagnosis and Complementary Examinations

The diagnosis is clinical by the history of high fever for 3–5 days that ceases with the appearance of the characteristic rash [33, 36].

In the acute infection, the presence of IgM antibodies confirms the diagnosis. In reactivation, the fourfold increase in IgG titers in sequential samples retrospectively confirms the diagnosis. In complicated cases or in immunocompromised patients, other techniques may be needed, such as PCR, electron microscopy, and viral culture, this being the gold standard in the active infection [33, 35, 36].

Leukocytosis, thrombocytopenia, and elevated transaminases in febrile phase followed by relative neutropenia and mild atypical lymphocytosis may be present.

Differential Diagnosis

The differential diagnosis is made with the diseases that present fever and rash, such as rubella, scarlet fever, measles, varicella, and erythema infectiosum.

Therapeutic Approach

The treatment consists of supportive care including antipyretics, since the disease often follows a benign and self-limited course. Hydration and hygienic care are also included [37].

Human Herpes Virus 7

Human herpes virus 7 (HHV-7) belongs to the genus Roseolovirus and subfamily Betaherpesviridae with tropism for CD4 T lymphocytes [38]. It is transmitted by saliva and its replication occurs in the salivary glands [33].

HHV-7 was originally isolated from T cells purified from the peripheral blood mononuclear cells of a healthy donor following incubation of the cells. It was then isolated from the peripheral blood mononuclear cells of a chronic fatigue syndrome patient and in healthy children and adults. Subsequently the virus was isolated in peripheral blood of one patient with exanthema subitum. Recent studies suggest a relationship between the virus and pityriasis rosea [33, 38, 39].

HHV-7 is a virus of global distribution and high prevalence in children under 6 years of age. Studies have reported the presence of the virus in the salivary glands and saliva of up to 80–90% of the population. The virus is related to HHV-6 in the etiology of exanthema subitum, and the involvement of both in pityriasis rosea has been suggested [33, 38, 39].

Studies linking HHV-6 and HHV-7 with pityriasis have involved tissue, whole blood, and serum analysis. Although some studies showed a clear association with HHV-6 and HHV-7, others found HHV-6 and HHV-7 to occur more commonly in controls than in persons with pityriasis. Given the nearly universal prevalence of HHV-6 and HHV-7, their association with pityriasis rosea remains under discussion. HHV-7 appears to have an association with lichen planus because of the more frequent presence of the virus in biopsy of lesions in healthy skin. It also may be related to graft-versus-host disease and DRESS syndrome [33, 38, 39].

Human Herpesvirus Type 8

Epidemiology

Human herpesvirus 8 (HHV-8, also known as Kaposi sarcoma–associated herpesvirus (KSHV)), is associated with the etiology of Kaposi sarcoma (KS) and other lymphoproliferative disorders, such as multicentric Castleman disease and pleural effusion lymphoma, and is most frequently found in immunocompromised patients, particularly by the HIV virus [40].

KS was first described in 1872 by Moritz Kaposi as a tumor of extremities among elderly men; this form became known as classic Kaposi sarcoma. KS was subsequently noted to be a relatively common tumor in sub-Saharan Africa in the 1950s–1970s, prior to the HIV epidemic [41].

In 1981, an unexpected increase of KS cases among young men who had sex with men in the United States was the harbinger of the AIDS epidemic. In 1994, HHV-8 was isolated from KS lesions in patients with HIV/AIDS, enabling the causal relationship between HHV-8 and KS to be established. At the start of the AIDS epidemic in the United States, between 20% and 50% of patients with AIDS developed KS and the disease is considered an AIDS-defining malignancy [41].

The incidence of KS associated with HIV declined significantly after the introduction of combination antiretroviral therapy (ART) in 1996, but remains the most common malignancy in HIV-infected patients. The classic form still occurs in regions endemic for HHV-8, and KS is still a serious public health problem in sub-Saharan Africa, where access to ART is restricted [40]. It now represents about 50% of tumors diagnosed in men in some central African countries [42].

Etiopathogenesis

The pathogenesis of tumors associated with HHV-8 involves the ability of the virus to infect lymphatic and vascular endothelial cells and induce the transcriptional reprogramming of certain human genes, many of which have immunologic and angiogenic properties. HHV-8 is the necessary but not sufficient cause for the development of KS, as only a small proportion of those infected by HHV-8 develop associated tumors [41].

In adults, the main mode of virus transmission is through sexual contact. Receptive anal intercourse is the main risk factor, since the seroprevalence of HHV-8 is larger in homosexual men than among HIV-positive women. The number of sexual partners proportionately increases the risk of acquiring the virus. Both

infected saliva and semen are carriers of the virus, with a much higher viral load for the former. In endemic areas, transmission occurs mainly during childhood, the nonsexual horizontal transmission being greater than the vertical route. Domiciliary living with those seropositive for HHV-8 and low socioeconomic and health status are important risk factors in this scenario. Less common but possible forms of transmission are through blood transfusion and solid organ transplants [2, 41].

Clinical Presentation

Four variants of KS are described: classic, HIV/AIDS-related, immunosuppression-associated, and African-endemic. All of them share the same cutaneous lesions: red, brown, or violaceous papules, plaques, and nodules, often associated with edema. However, they have different presentations and clinical courses [2].

The typical patient with classic KS is an elderly man of Mediterranean or eastern European descent who presents with multiple discrete red to blue-purple or black patches on the lower extremities. The lesions can initially appear as bruises. Early macules or patches coalesce into characteristic plaques and nodules and can later become brown, hyperkeratotic, and/or eczematous. In its classic form, KS can be considered a benign neoplasm because affected persons tend to die of other causes [33].

There are four subtypes of African-endemic KS: nodular, lymphadenopathic, florid, and infiltrative. The nodular subtype is characterized by a small number of well-circumscribed cutaneous nodules and typically has an indolent course in young adults (Figs. 10.8a, b and 10.9a–c). The fulminant lymphadenopathic subtype predominantly affects the lymph nodes of children and is often fatal. The florid and infiltrative forms frequently have a large number of cutaneous lesions on one or more extremities. These latter two types are aggressive and may spread deeply into the subcutaneous tissue, muscle, and bone [2].

AIDS-related KS typically presents as more widely distributed macules, patches, or plaques (Fig. 10.10a, b), which occasionally become exophytic or ulcerative. Involvement of the oral cavity and face occurs more often than in classic KS
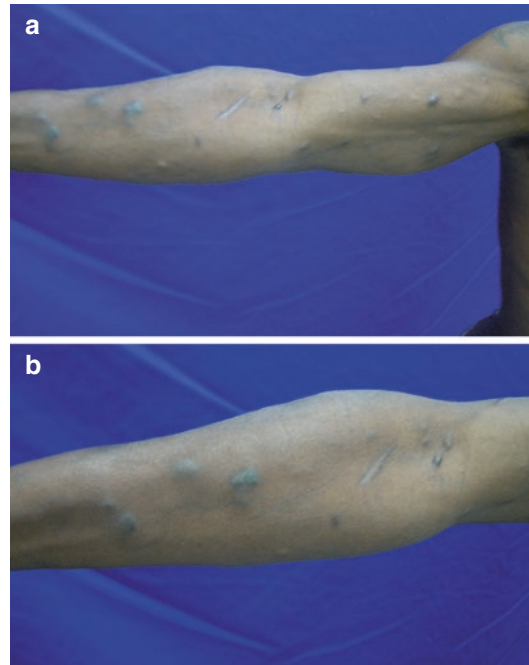
Fig. 10.8 (**a, b**) Kaposi sarcoma in an HIV-negative patient

and may be one of the first indications of HIV infection. Involvement of the genital mucosa, lungs, and gastrointestinal tract (particularly the stomach and duodenum) is common. Approximately 80% of AIDS patients with KS develop gastrointestinal involvement. Oral lesions can cause significant discomfort as well as difficulties with speech and eating; gastrointestinal involvement may lead to nausea, vomiting, bleeding, perforation, and/or ileus; and pulmonary involvement can result in persistent cough, bronchospasm, or dyspnea. AIDS-related KS has a variable clinical course, and prognosis is generally related to the degree of immune impairment and overall health of the patient. However, flares of KS can occur as a manifestation of immune reconstitution following initiation of ART [2].

KS associated with immunosuppression develops in patients after solid organ transplantation or the use of immunosuppressive therapy for various diseases. The cutaneous presentation resembles that of classic KS, but the site of manifestation is much more variable. It is more aggressive by nature and tends to affect lymph
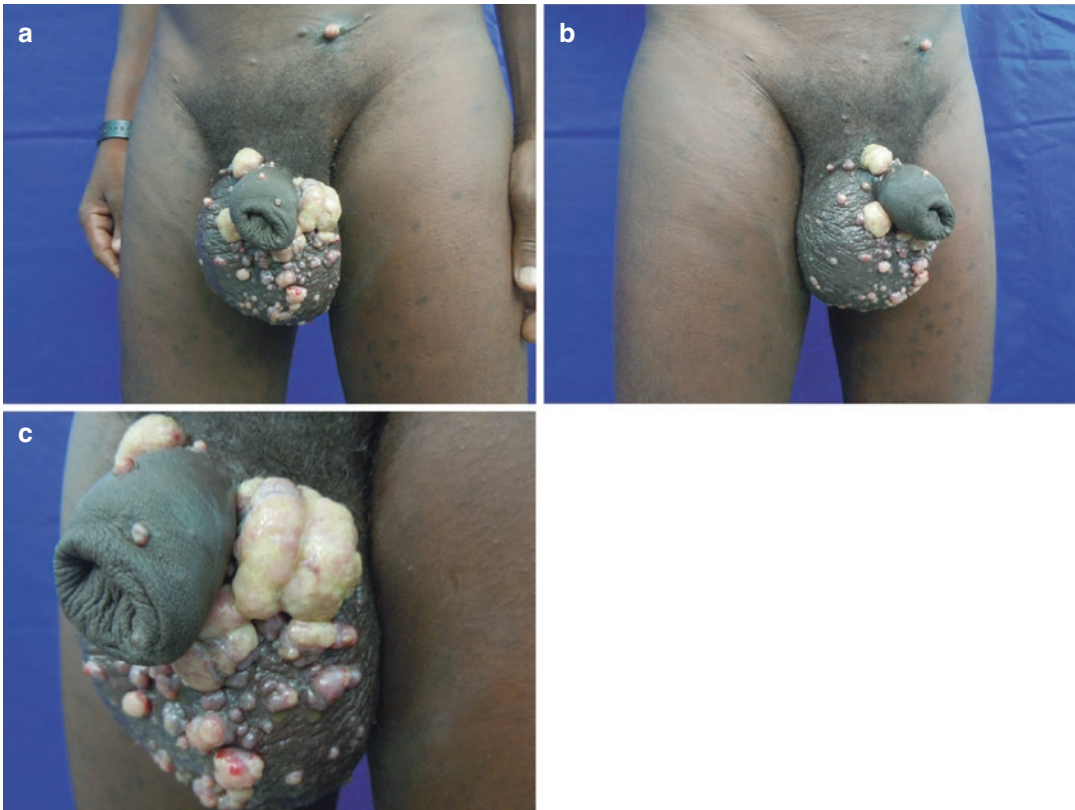
Fig. 10.9 (**a–c**) Same patient shown in Fig. 10.8, 1 year later

Fig. 10.10 (**a, b**) AIDS-related Kaposi sarcoma

nodes, mucous membranes, and viscera, even in the absence of detectable cutaneous lesions [42]. However, as is the case for AIDS-associated KS, the prognosis for patients with transplant-associated KS is also much poorer than that for patients with classic KS [33].

Diagnosis

Biopsy is required for definitive diagnosis. Characteristic angioproliferative histologic features include a variable combination of spindle-shaped cells, aberrant proliferation of leaky blood vessels with extravasated erythrocytes,

and inflammatory infiltrates, in accordance with the stage of development of the lesions. Immunohistochemical staining of biopsy specimens is generally performed to confirm diagnosis by detection of antibodies against latent nuclear antigen (LANA) within the spindle cells. KS spindle cells are proliferating KSHV-infected endothelial cells that have undergone reprogramming and differentiation [41].

> **Box 10.3 Diagnosis of KS**
> The diagnosis of KS is confirmed by biopsy of the suspected cutaneous lesion. Serology for HHV-8 is not required

Complementary Examinations

The complete physical examination with inspection of the oral cavity and occult blood in the stool are essential for all patients. Those who present gastrointestinal symptoms, positive occult blood in the stool, or unexplained iron-deficiency anemia should undergo endoscopic examination of the digestive tract. Patients with respiratory symptoms should undergo imaging of the thorax and fiberoptic bronchoscopy, and patients with lymphadenopathy or B symptoms should undergo cervical, thoracic, abdominal, and pelvic tomography to search for lymphadenopathy or lymphoproliferative neoplasm associated with HHV-8 [41].

Differential Diagnosis

The differential includes acroangiodermatitis (pseudo-Kaposi sarcoma), bacillary angiomatosis, ecchymosis, hemangioma, angiosarcoma, pyogenic granuloma, and pseudolymphoma/lymphoma [2].

Therapeutic Approach

The objective of the specific therapy for KS for all patients is to improve symptoms and quality of life and slow the disease progression. For patients with KS associated with AIDS or any other immunosuppression, correcting immune deficiency when possible is recommended. ART for viremia control is mandatory and may

be sufficient in HIV-positive patients with limited disease. In immunocompetent patients with limited disease, few symptoms, and slow progression, the strategy can be expectant. Localized symptomatic lesions can be addressed with intralesional injection of vinblastine or interferon-α (IFN-α), topical alitretinoin, liquid nitrogen, laser therapy, or radiotherapy.

Surgical intervention is rarely indicated, except to make a pathological diagnosis or to remove or debulk a single lesion that is dangerous or particularly symptomatic by virtue of its location (e.g., urethral or airway obstruction). Systemic therapy is indicated in cases of extracutaneous involvement and in rapidly progressive cutaneous disease, voluminous cases or those that causes pain, lymphedema, functional limitation, or emotional stress. Liposomal anthracyclines (doxorubicin or daunorubicin) are first-choice therapies. The second line of therapy uses paclitaxel and alternatives include vincristine, vinblastine, vinorelbine, etoposide, and bleomycin. IFN-α, interleukin (IL)-2, thalidomide, and others that target KS and immunomodulatory approaches have been evaluated. The best-studied agent, IFN-α, is a cytokine with immune-modulatory, antiviral, and antiangiogenic activity. In HIV-associated KS it is best utilized for patients with limited disease and preserved CD4 counts. Antiherpetic agents have not been shown to have activity in treating established KS [41].

Human Papillomavirus

Introduction

Papillomaviruses are a large group of DNA viruses that are widely distributed in animals and humans. By infecting the basal cells of the epithelial mucosa, papillomaviruses cause malignancies (cervical, penile, vulvar, vaginal, anal, and oropharyngeal) and noncancerous cutaneous manifestations. Noncancerous cutaneous manifestations include common warts (verruca vul-

garis), plantar warts, plane warts, and anogenital warts. Cutaneous and anogenital warts are common reasons for a dermatology office visit. Although there are various therapies available, they are extremely difficult to treat and none of the treatment modalities are curative [43].

STDs caused by human papillomavirus (HPV) are discussed in Chapter 9.

Epidemiology

Cutaneous warts occur more in children, adolescents, and young adults, with its prevalence estimated to be between 3% and 20% in schoolchildren. The HPV virus is found globally, and its transmission occurs by direct interpersonal contact and indirect contact through contaminated objects and surfaces, such as swimming pool surrounds [44, 45]. The presence of lesions in individuals of the same school or family is frequent, with the frequent observation of more infected individuals in the same household [46]. Transmission also occurs by self-inoculation of HPV from affected areas to healthy and perilesional areas. They also have clinical importance in the immunocompromised, in whom the lesions tend to be more extensive and of a more prolonged course [45].

Etiopathogenesis

HPV is a nonenveloped, double-stranded DNA virus. The capsid has a viral coverage that, besides being the protection of the viral DNA, allows their binding to target cells in the infection process. The virus enters the epithelial basal cells by microabrasions in the most superficial skin layers, which serve as a mechanical barrier to the penetration of the microorganism [44, 45].

After penetration of the basal keratinocytes, the viral DNA is incorporated into the genomic material of the cell, initiating replication. The cellular immune response is the most important pathway in the immune control of the HPV infection, which explains the persistence of infection and more exuberant lesions in patients deficient

Table 10.6 HPV subtypes related to nonanogenital cutaneous disease

Cutaneous disease	HPV types associated most frequently detected
Common warts	1, 2
Flat warts	3, 10
Epidermodysplasia verruciformis (EV)	3, 5, 8
Heck's disease (focal epithelial hyperplasia)	13, 32
Oral papillomas	2, 6, 7, 11

in this response, such as those infected with HIV. Up to 90% of the cutaneous warts disappear spontaneously within 2 years [45]. The humoral immune response does not seem to play an important role in the immune control of the infection.

To date, more than 120 different types of HPV are known and completely characterized. The types 1, 2, 4, 7, 27, and 57 are the most commonly detected in common, plantar, and palm warts, whereas types 3 and 10 are associated with flat warts [45, 47] (see Table 10.6).

Some types have oncogenic potential, such as HPV-5 and -8, related to the development of squamous cell carcinoma (SCC) in patients with epidermodysplasia verruciformis, a predisposing condition addressed below, in addition to those associated with anogenital malignancies (discussed in another chapter).

Clinical Presentation

• *Common warts*: Common warts are usually exophytic, multiple, irregular, rough nodules that show a variety of clinical patterns at different sites of trauma particularly on fingers, but also on other frequently rubbed and abraded skin surfaces such as hands, elbows, and knees (Fig. 10.11a–e). They range from small papules to large, hyperkeratotic, fissured, cauliflower-like lesions [45]. Black dots corresponding to thrombosed capillaries are typical findings on dermoscopy, and an important clue for diagnosis. Filiform warts can occur in periorificial areas of the face. (Fig. 10.11f) "Butcher's
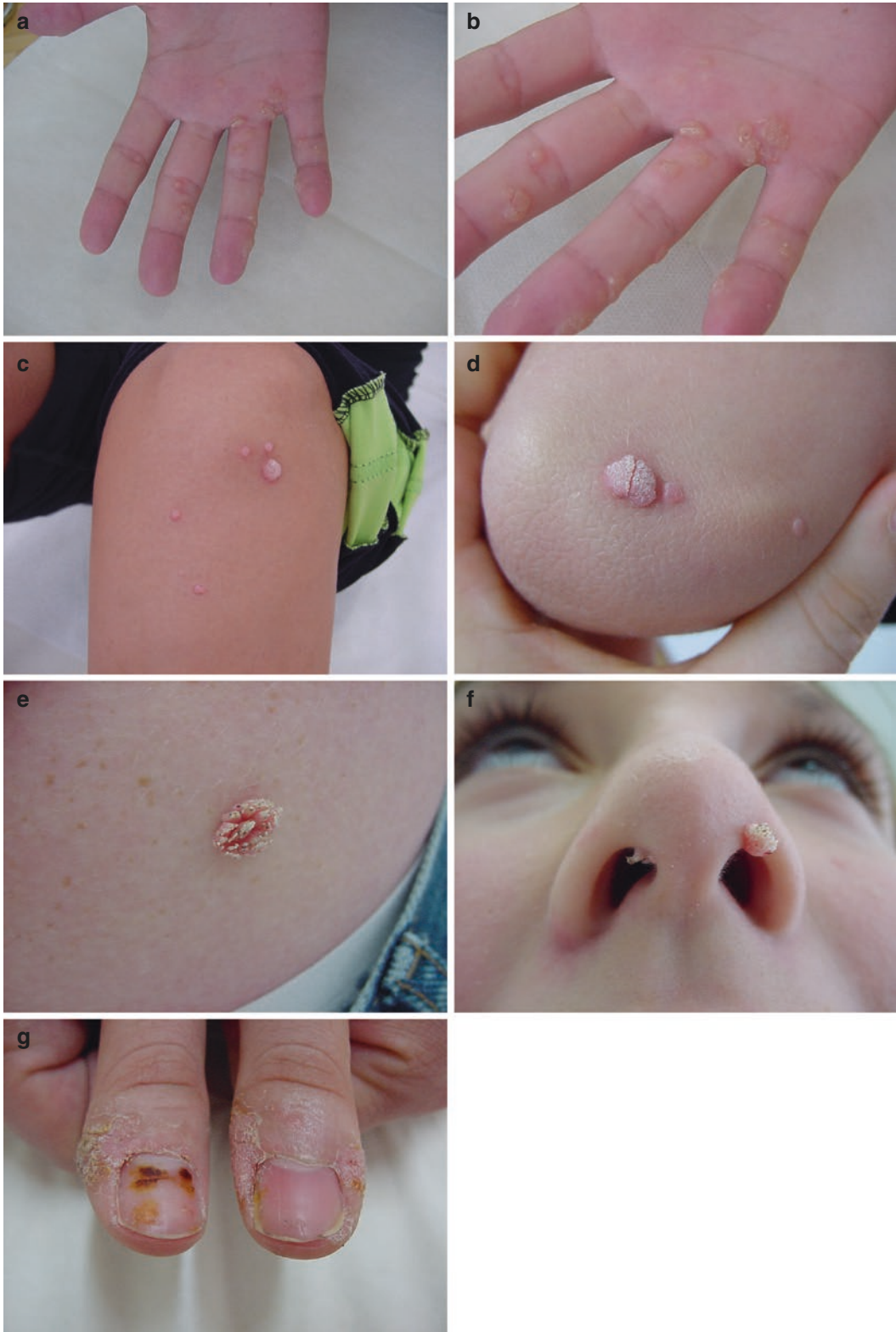
Fig. 10.11 (**a–e**) Common warts. (**f**) Filiform warts in periorificial locations on the face. (**g**) Periungual warts
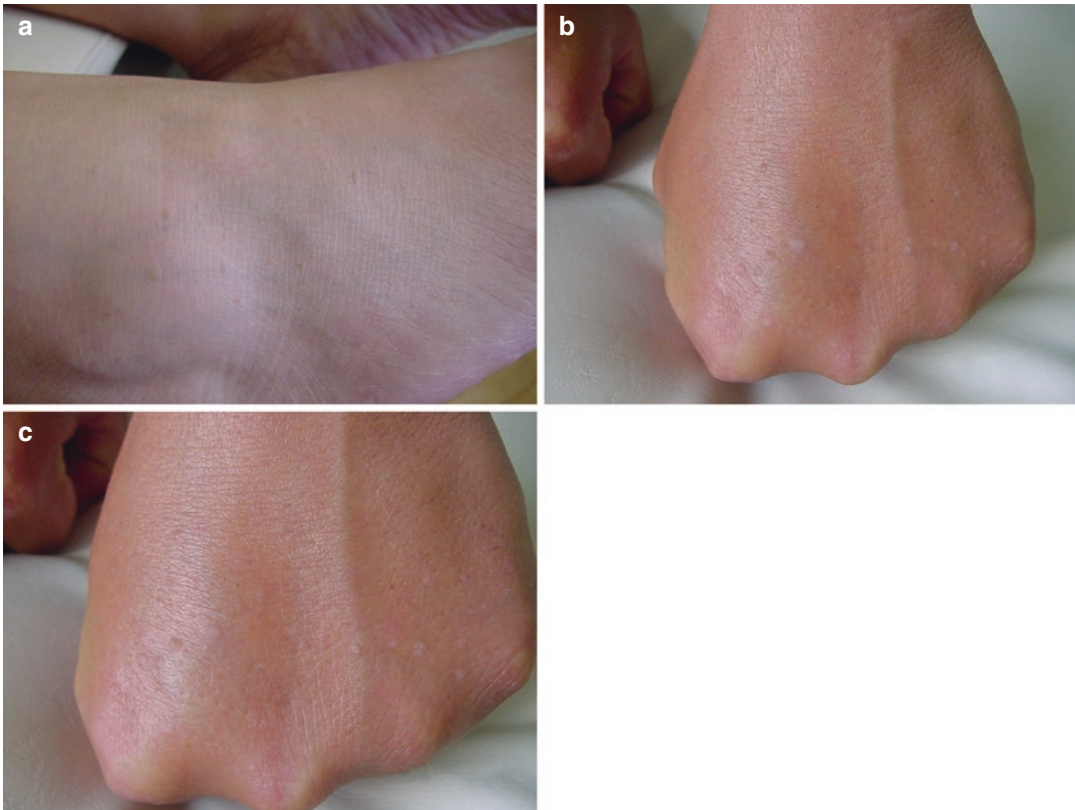
Fig. 10.12 (**a–c**) Flat warts

warts" occur in professionals who deal with the processing of meat and fish. Warts are extensive on sites of trauma, such as fingers and the periungual area, and are related to HPV-7 [44, 45] (Fig. 10.11g).

- *Flat warts***:** Skin-colored papules or slightly hypochromic or pinkish, slightly elevated, flat lesions usually located on the face, back of the hands and feet, and arms. These warts are common in children and in adult women. There may be a phenomenon of regression of the lesions, preceded by rash and swelling in the affected areas [45] (Fig. 10.12a–c).
- *Palmoplantar warts*: Hyperkeratotic papules with deep inward growth, slightly raised edges, and depressed center (called "myrmecia") (Fig. 10.13a–c). They cause significant pain when walking due to pressure on the affected sites. Thrombosed capillaries are found and effect differentiation with palmarplantar calluses. The warts may coalesce to

form mosaic warts [44] (Fig. 10.13d–f). They rarely occur in children younger than 5 years [45].

- *Epidermodysplasia verruciformis*: A rare autosomal recessive genetic disorder whereby there is a susceptibility to infection with certain types of HPV that commonly do not produce clinical lesions in individuals without the disease. Types 5 and 8 are most often related to the development of skin cancers, especially on sun-exposed areas [45]. Characteristically patients have widespread papular lesions that are confluent, flat, and pink, often resembling tinea versicolor, but may present diverse types of skin warts. Early-appearing lesions of actinic keratosis gradually transform into squamous cell carcinoma (Fig. 10.14a–d).
- *Oral papillomas*: The most common benign tumors of the oral mucosa. Common warts can spread from the hands to lips by finger

Fig. 10.13 (**a–c**) Myrmecia. (**d–f**) Mosaic warts

Fig. 10.14 (**a–d**) Epidermodysplasia verruciformis

Fig. 10.15 (**a**, **b**) Warts on hands and lips of the same patient

Fig. 10.16 Common warts on the oral mucosa

sucking and nail biting, with cutaneous HPV types identified in the lesions (Fig. 10.15a, b). They can become warty on the tongue and hard palate which has a stratum corneum. Other HPV-induced oral lesions include common warts on the oral mucosa associated with HPV-2 (Fig. 10.16), and the multiple soft papules of Heck's disease (focal epithelial hyperplasia) found most commonly in Eskimos and North American Indians and associated with HPV-13 or -32 [45].

Diagnosis and Complementary Examinations

In most cases, the diagnosis of the cutaneous warts is carried via dermatologic examination. With the aid of dermoscopy it is possible to see

the darkened points on the corresponding lesion to thrombosed capillaries, typical of HPV lesions. Anatomopathologic examination, viral typing, or other complementary tests are used in doubtful cases or to exclude dysplasia or malignancy.

Differential Diagnosis

The main differential diagnoses to consider are actinic keratosis, cutaneous horn of other etiologies, SCC, keratoacanthoma, palmoplantar calluses, hyperkeratotic lesions related to psoriasis and hypertrophic lichen planus, and palmoplantar keratoderma. Flat lesions can frame differentiation with Gottron's papules of dermatomyositis, as well as lichen planus or lichen sclerosus [44].

Therapeutic Approach

For the therapeutic approach to lesions, each patient and case should be individualized taking into account the number of lesions and their location, the patient's pain tolerance, risk of scarring, and cost to the patient in addition to the experience of the professional.

There are numerous treatment modalities, although there are few well-designed studies in the literature supporting their use (see Table 10.7).

In minimally symptomatic lesions in an immunocompetent patient, only an expectant approach can be maintained because of the possibility of spontaneous regression. Symptomatic, unaesthetic lesions in immunocompromised patients or those at risk for malignancy can be treated by a variety of therapies [48].

There is no antiviral treatment that is specific for HPV, but some of the available therapies interfere with the viral life cycle. The most common approach to treatment is to damage or destroy the infected epithelium. This can also induce cell death and antigen exposure and presentation, thereby potentially inducing an immune response.

Destructive Chemical Agents

Salicylic acid (SA) is the most commonly used formulation for skin wart treatments for which studies with a higher level of evidence exist. SA promotes exfoliation of epithelial cells. It is an

Table 10.7 Classification of the main therapeutic agents for cutaneous warts

Destructive chemical agents
Salicylic acid
Trichloroacetic acid
Glycolic acid
Cantharidin
Phenol
Silver nitrate
Destructive physical agents
Cryotherapy (liquid nitrogen)
Curettage
Electrodesiccation/electrocautery
Excision
Laser (pulse dye, Nd:YAG, CO_2)
Photodynamic therapy
Antiproliferatives
Podophyllin/podophyllotoxin
5-fluorouracil
Bleomycin
Retinoids
Immunostimulants
Imiquimod
Zinc sulfate
Intralesional immunotherapy
Diphencyprone

irritant at high concentrations, which can promote an additional effect of stimulating the immune response of an affected individual [48]. It is used in a variety of vehicles (collodion, ointments, gels, patches, and creams in concentrations of 10–50%). SA can be associated with other keratolytic substances, most commonly with lactic acid between 4% and 17% [49]. Variations in the form of application, concentration, and solvent vary according to the kind of wart. In plantar or thicker common warts, the treatment is optimized with prior mechanical exfoliation with sanding of the region to be treated. One should be careful to protect the skin around the lesion before application to avoid irritation and erosions.

Trichloroacetic acid is classically used to treat genital warts, with little evidence for use in nongenital warts [43, 48].

Other chemical agents are described in the treatment of skin warts, but with a lower level of evidence in the literature, such as cantharidin, phenol, 10% silver nitrate, 5% glycolic acid, 70% pyruvic acid, citric acid, and formic acid [48].

Destructive Physical Agents

- *Cryotherapy*: This is the most commonly used form of treatment for skin warts. Liquid nitrogen or even carbon dioxide are utilized. It can be applied by spray or contact with a cotton swab, with evidence showing equal efficacy between both [48]. It causes irreversible damage to cell membranes by freezing, with inflammation and stimulus of cellular immune response. In general, the application should be maintained for 10–30 s, depending on the treated region, followed by formation of a perilesional halo of about 1–2 mm. The freezing time ranges from 10 to 15 s up to 30 s or more in more aggressive applications. After thawing, the application is repeated. An interval of 2–3 weeks between each application is recommended until complete resolution [49]. Its efficacy is comparable with that of SA, and there is evidence showing optimum results with the combination of both therapies. Adverse effects include pain during the application (limiting its use in children), discomfort by postapplication inflammation (patients should be alerted to the occurrence of blisters and erythema), hyper- or hypochromia (especially in patients with high skin phototypes), and scarring [48].
- *Surgical treatment*: Manual curettage, electrodesiccation, electrocautery, and conventional resection are alternatives in localized and resistant lesions. Curettage is a method widely employed for plantar warts, and may be combined with other treatments for best results.
- *Laser*: Pulsed dye laser at 585 nm acts in the blood vessels of the warts and also by thermal injury to HPV. The use of CO_2 laser and Nd:YAG is also described in a few studies. Combination therapies before and after laser treatment, such as with bleomycin and SA, have been described [48, 49].
- *Photodynamic therapy*: Studies with different protocols suggest the efficacy of treatment using 10–20% aminolevulinic acid [48]. A significant adverse effect during the procedure is pain.

Antiproliferatives

- *Podophyllin and podophyllotoxin*: The first is no longer recommended because of its potential toxicity and considerable local irritation. Podophyllotoxin, the active component of podophyllin, is still used for the treatment of anogenital warts, but has limited use in skin warts. The assumption is that penetration of the thick, cornified layer of cutaneous warts is poor compared with that achieved at mucosal sites [43, 48].
- *5-Fluorouracil*: this agent blocks the synthesis of DNA, damaging the cell division of basal cells. It can be used as a cream in a concentration of 5% for 4–12 weeks, with better results if used under occlusion. It may be associated with 10% SA [49]. Association with cryotherapy does not appear to improve results. It can cause severe irritation and erosions in the treated areas, with subsequent formation of hyperpigmentation or, less frequently, hypopigmentation [48].
- *Bleomycin*: This is a systemic chemotherapeutic agent that has also been used through an intralesional pathway in warts, although its management is very painful and produces necrosis in the applied region which can be excessive [48]. The wart cure rate is very variable (14–99%) [43].
- *Retinoids*: These agents act on the replication and differentiation of keratinocytes, reducing viral replication and reducing the thickness of the lesions. They can be used topically, such as adapalene and tretinoin in flat warts, while isotretinoin and acitretin are used orally for immunosuppressed patients with severe disseminated warts [48].
- *Cidofovir*: A nucleoside analog that inhibits viral replication. It is used topically, with some reports of systemic use in the immunocompromised. Cream containing 1–3% can be used five times a week every other week for about 8 weeks [48]. It seems to be well tolerated topically, but systemic use can cause nephrotoxicity and neutropenia. Its use is off-label for the treatment of skin warts [43].

Immunostimulants

- *Imiquimod*: Well-known for the treatment of anogenital warts, its use is described for the treatment of persistent nongenital skin warts or therapeutic failure by other methods. It stimulates the inflammatory response against infected keratinocytes by inducing IFN-α, IL-12, and tumor necrosis factor α, with NK cell stimulation. Studies with a lower level of evidence showed over 50% improvement in lesions with applications two times a day for a maximum of 24 weeks. It is generally used in

a 5% cream [43, 48]. The side effects are discomfort through irritation and erosions in the application region during the treatment.

- *Zinc sulfate*: The mechanism of action of this agent is not well established, but it is known that zinc plays an important role in leukocyte function and NK cell activity. It can be used topically or systemically, although without consistent studies in the literature evaluating its use. Described treatments are topical from 5% to 20% [48] and oral supplementation (10 mg/kg/day) [8, 43].
- *Diphencyprone*: This agent induces local hypersensitivity, stimulating the immune response against the HPV lesions. Its efficacy has been shown in some retrospective studies. It may provoke erythema, desquamation, itching, and discomfort, and in some cases allergic contact eczema beyond the area of application [48].
- *Intralesional immunotherapy*: Mumps, *Candida*, and *Trichophyton* antigens are allergenic extracts that are thought to act by inducing a delayed hypersensitivity reaction. A review found clinical resolution after local injection into the base of warts, with remission rates of 60% for mumps/*Candida*/*Trichophyton*, 82% for *Candida*, and 84.6% for measles, mumps, and rubella. Advantages of this method include lack of scarring and minimal pain. Disadvantages include erythema at the injection site, and systemic effects such as fever and myalgias [49].

Enterovirus

Introduction

Enteroviruses are composed of about 70 serotypes belonging to the Picornaviridae family, and are present worldwide. These viruses are responsible for a wide spectrum of diseases and usually affect children [50].

Epidemiology

Enteroviruses are ubiquitous and can cause illness in any age group, but are more common in children 1–4 years of age [51].

Enterovirus infections (enteroviruses) may occur throughout the whole year, but the largest number of cases and epidemics occur in the summer and fall. The highest-risk groups are children and those who live in settlements of low socioeconomic status [50].

Etiopathogenesis

Enteroviruses are small, single-stranded RNA viruses, nonenveloped, of the Picornaviridae family. They are composed of about 70 serotypes, including echovirus, coxsackievirus A and B, enterovirus 68–71, and poliovirus. They cause various diseases, some having tropism for certain tissues, but not of specific form.

Transmission occurs between humans through a fecal-oral pathway, respiratory pathway, and from mother to child during and after birth. The incubation period ranges from 3 to 6 days [50, 52]. After the initial contact, through the respiratory mucosa or lower digestive tract, the virus replicates in the lymphoid tissues and spreads through the blood, causing low-level viremia. Subsequently, the virus reaches the CNS, heart, liver, lungs, adrenal, and skin, transitioning to the phase of clinical symptoms. When the virus replicates in these sites, the phenomenon known as high-level viremia occurs [50, 52].

Clinical Presentation

The clinical manifestations of infection by enterovirus are quite varied, from a simple respiratory infection to aseptic meningitis. Among the mild infections one observes fever with or without rash, hand-foot-mouth syndrome, herpangina, pleurodynia, pharyngitis, conjunctivitis, and croup. Among the serious infections, meningitis, encephalitis, acute palsies, neonatal sepsis, myocarditis, pericarditis, hepatitis, and chronic infections in immunosuppressed patients have been reported [51].

Hand-Foot-Mouth Disease
Hand-foot-mouth disease is caused by various strains of enterovirus, most commonly by coxsackie A16 virus (CAV16) and enterovirus 71 (EV71), and mainly affects children under 10 years

of age. The disease can present prodrome of fever, malaise, coughing, loss of appetite, abdominal pain, myalgia, or fever odynophagia for 12–36 h. It is usually self-limited, resolving in 48 h [53]. One to 2 days after the onset of disease painful lesions appear in the mouth, tongue, palate, anterior tonsillar pillars, and oral mucosa. When broken these vesicles form painful ulcers that resolve in 5–7 days [52, 53]. After the appearance of oral lesions, vesicles arise with adjacent erythema on the hands and feet (Fig. 10.17a–c), which are not itchy and may be painful, resolving in around 7–10 days.
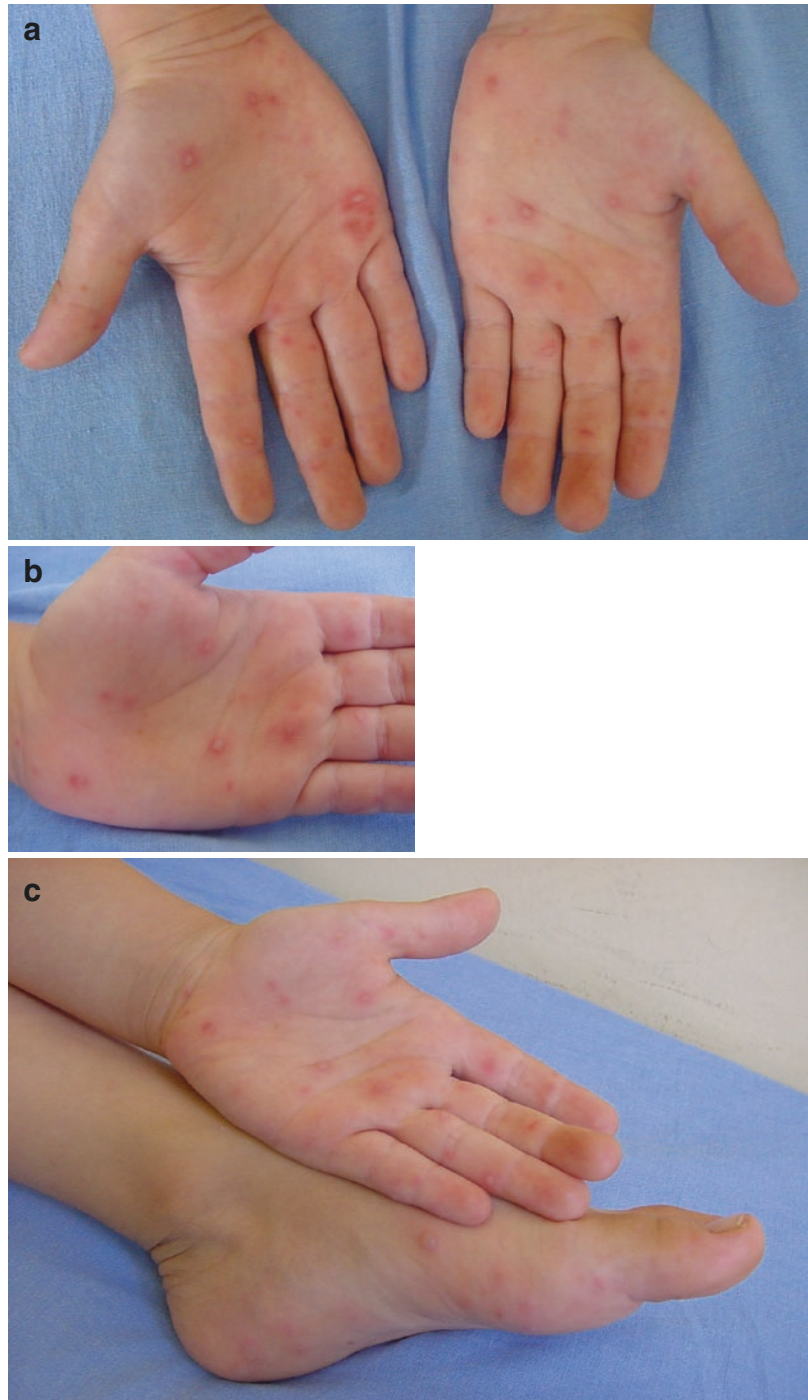
Fig. 10.17 (**a–c**) Vesicles on the hands and feet

Less commonly these lesions can be nodules, papules, or vesicles grouped and located in the gluteal and genital regions.

Complications are uncommon and involve the cardiopulmonary and neurologic system. Onychomadesis may persist for up to 4 weeks after infection because of the arrest of ungueal matrix growth [53].

Herpangina

Another frequent enterovirus, herpangina has coxsackievirus A1–A6, A8, A10, and A22 as the most common viruses, although it can also be caused by coxsackievirus B1–B4, echovirus, and other enteroviruses. The incubation period varies from 1 to 10 days [52]. It affects children aged 3–10 years with prodrome of fever, headache, malaise, and pain in the cervical region, followed by the appearance of painful oral lesions in 2–3 days. These are usually papules, which evolve into vesicles, and later ulcers in the soft palate, uvula, tonsils, pharynx, and oral mucosa, accompanied by erythematous pharyngitis. The fever usually has spontaneous remission in about 4 days and oral lesions in around 7 days [52].

Diagnosis and Complementary Examinations

The presumptive diagnosis is made by clinical signs and symptoms, season of the year, geographic location, and contact history [52].

Diagnostic confirmation can be reached by culture, serology and PCR. The main indication of confirmation is in cases of complications. The virus is found in the oropharynx, blood, cerebrospinal fluid, urine, and the tissues affected by the disease. Culture plays an important role in the epidemiology once it can identify the virus serotype. However, it is scarcely applied in practice because of the time required (4–8 days) to obtain the result, which is unhelpful for treatment decisions in daily practice.

Serology has limited usefulness because of the time required for the result and the diversity of the serotypes.

PCR is the method of choice in the diagnosis because of its high sensitivity and specificity; besides being rapid, it requires small samples and detects the virus in the cerebrospinal fluid [52, 53].

Differential Diagnosis

The differential diagnosis is broad and is performed according to the clinical manifestation of the enterovirus. It includes papular urticaria, impetigo, measles, rubella, scarlet fever, roseola, pityriasis rosea, aphthous stomatitis, erythema multiforme, herpetic gingivostomatitis, drug eruption, and other forms of herpesvirus infection.

Therapeutic Approach

The majority of diseases caused by enterovirus are self-limiting, so the main treatment consists of supportive measures and more intensive measures in cases of complications.

In serious infections caused by EV71, in vitro studies showed benefit from the use of IgG, IgG3 subclass [53]. Pleconaril, an antiviral that acts on protein binding of the viral capsid and has a broad spectrum, has been studied for use in severe infections and showed satisfactory results [54].

Measles

Introduction

Measles was first described as an entity distinct from other rashes in 900 BC by the Persian physician Muhammad Rhazes [36].

It is an extremely contagious exanthematous viral disease distributed worldwide. After the introduction of the vaccine in 1963, the profile of incidence, morbidity, and mortality decreased dramatically, but persists within the ten most infectious diseases of highest mortality in the world [52, 55].

Epidemiology

A disease of worldwide distribution, more common in children and highly contagious, measles can be considered endemic and epidemic in the European, African, and Asian continents and features outbreaks in America [55].

The elimination of measles in the United States occurred in 2000 and since then there have been no epidemics, but the number of cases appears to be increasing in recent years: from January to November of 2015, 189 cases were reported. Of these, the highest percentage is in the age group between 20 and 39 years and the most affected did not have the vaccine or were unaware of the status of vaccination. The vast majority of cases were associated with patients from endemic countries [55].

Data from Canada, from the period 2002 to 2013, show an incidence of 0.29 cases per 100,000 people. In 2011, Brazil notified 18 cases brought to the exterior. In Europe there were 27,134 cases from January 2014 to March 2015.

In Africa, in 2013, data from the Democratic Republic of Congo, Nigeria, Angola, and Uganda showed 158,361 cases. In Asia the 2014 data, including suspected and confirmed cases, demonstrated 112,483 in China, 58,010 in the Philippines, and 18,597 in Vietnam [56].

The risk of infection is associated with contact between people who have traveled or travel to endemic or epidemic areas. In temperate climates, epidemics usually occur in late winter and early spring and in tropical climates, during the period of rainfall. However, the main risk of contamination occurs in patients who have not undergone vaccination. Data show that a substantial proportion of measles cases the United States in the era after elimination was intentionally unvaccinated [52].

Etiopathogenesis

Measles is caused by an RNA virus, enveloped, single-stranded, with 19 genotypes of the Paramyxoviridae family and a member of the genus Morbillivirus [36]. It has two membrane proteins that mediate entry into the host cell, the hemagglutinin that fixes the virus in host cell and fusion proteins, responsible for the fusion of the viral membrane into the cell, virus penetration, and hemolysis.

Contact with the virus occurs through the air from one person to another, via large droplets of saliva, and, less commonly, via small aerosol particles when coughing, sneezing, talking, or breathing.

The expelled virus can stay alive for up to 2 h on a surface or in the air. Man is the reservoir and the source of infection. The incubation period ranges from 7 to 18 days, with an average of 10 days until the onset of fever and 14 days until the onset of the rash.

The transmission period is 4 days before the onset of the rash to 4 days after the disappearance, although immunosuppressed patients can transmit the virus for more prolonged periods [55].

Penetration occurs in the mucosa of the upper respiratory tract. Viral replication starts at this site and in the lymph nodes, causing the first viremia after 2–3 days. The virus reaches the reticuloendothelial system, where it spreads after 5–7 days in a second viremia to the respiratory tract and other organs. Mothers, previously vaccinated, may pass antibodies to newborns through immunity induced by the vaccine [57].

Clinical Presentation

Measles has two clinical presentations, classical and atypical [36].

Classic measles has an evolution in stages. In the prodromal period, about 10 days after infection, the patient presents with fever, productive cough, coryza, nonpurulent conjunctivitis, photophobia, slight increase in cervical lymph nodes, abdominal pain (caused by the increase in intraabdominal lymph nodes), and the appearance of white spots with an erythematous halo in the oral mucosa, known as Koplik's sign. Koplik's sign is pathognomonic of measles and may arise in the days before the rash or after its appearance.

The second stage is the exanthema, which appears 2–4 days after the onset of fever, while other symptoms are accentuated. It is characteristically maculopapular, reddish, and with a cranial-caudal distribution. It starts in the retroauricular region and face and spreads to the trunk and extremities, lasting 5–6 days.

The third phase is the period of convalescence or furfuraceous desquamation, when the stains disappear through a fine desquamation, disappearing in the same order they appeared. Anorexia, diarrhea, and lymphadenopathy may also be present [52].

Atypical measles occurs in individuals with partial immunity to the virus, when exposed to wild-type virus. It has been reported in patients who received inactivated (or killed) measles vaccine (used in the 1960s), or persons who were given attenuated (weakened) live measles vaccine that was, by accident, inactivated during improper storage, in unvaccinated and immuno-compromised patients. It presents fever, pneumonia, pleural effusion, edema, and exanthema, maculopapular or petechial, with initial appearance in the extremities, hands, and feet [36].

Complications occur in up to 40% of patients, and the factors that increase risk are:

- Age: children under 5 years of age (especially in children <1 year) and people over 20 years of age
- Malnutrition
- Immunosuppression
- Gestation

The most common complications are bacterial respiratory tract infections (otitis media and pneumonia), pneumonia being the leading cause of death in children. Subacute sclerosing panencephalitis is a delayed neurodegenerative disorder that can occur as a complication of measles many years after the acute disease. It is characterized by seizures, personality changes, coma, and death [55].

Diagnosis and Complementary Examinations

The diagnosis of measles is based on clinical and epidemiological findings. The Table 10.8 summarizes the situations where one should suspect a case of measles. Outside of an outbreak of the disease, it should be confirmed by laboratory examinations.

The diagnostic test considered the gold standard is the evaluation of serum IgM antibodies, which can be detected in acute infection after

3 days of exanthema onset, becoming undetectable after 30 days.

The detection of IgM antibodies in oral fluids is an option with specificity comparable with that of the blood test, but with a slight reduction in sensitivity.

Increase in IgG titers of more than fourfold in sequential samples also confirms diagnosis.

The reaction by PCR is another alternative for confirmation, which uses the material collected by nasopharyngeal swab, blood, or urine from 1 to 3 days after exanthema onset up to a maximum of 7 days [55, 57].

Differential Diagnosis

The differential diagnosis is made with other diseases with maculopapular exanthema, such as rubella, infectious erythema, roseola, enteroviruses, infectious mononucleosis, cytomegalovirus infection, staphylococcal toxic shock syndrome, scarlet fever, Kawasaki disease, acute HIV infection, dengue, secondary syphilis, and hepatitis B.

Therapeutic Approach

Treatment

Treatment consists of supportive care, since there is no recommended specific antiviral therapy.

Hydration, nutritional support, hygiene of the eyes, skin, and airway, and antithermic medication are options. In cases of complications such as pneumonia or otitis media, antibiotics should be used [52].

The World Health Organization (WHO) recommends the use of vitamin A for children in developing countries, as its use is associated with decreased mortality and morbidity. It should be administered once a day for 2 days; the recommended doses are summarized in the Table 10.9 [58].

Table 10.8 When to suspect and test for measles

Typical or atypical clinical presentation	Unvaccinated
	Unknown vaccination status
	Residence or travel to endemic area
	Living/residence in agglomerations

Table 10.9 Recommended doses of vitamin A

Children under age 6 months	50,000 IU/day
Children between the ages of 6 and 11 months	100,000 IU/day
Children 12 months of age or more	200,000 IU/day

Vaccination

The vaccine against measles is a combination that besides measles also protects against rubella and mumps (MMR). The child should receive two doses, the first between 12 and 15 months of age and the second from 4 to 6 years of age [6]. There are currently MMR options associated with varicella vaccine (MMRV), which can be administered in children 1–12 years of age, and the current recommendations are employed in the second dose [6]. Pregnant women, immunocompromised patients, and patients with history of anaphylactic reaction to neomycin should not receive the vaccine.

The MMR vaccine is recommended as postexposure prophylaxis in persons 12 months of age or older, preferably within 72 h after initial contact. Patients who have received only one dose of the vaccine can receive the booster after exposure within 72 h. Immunoglobulin is recommended as postexposure prophylaxis for up to 6 days after initial contact in children under 12 months of age, pregnant women without evidence of immunity, and immunocompromised patients. The administered dose is 0.5 ml/kg intramuscularly or 400 mg/kg intravenously [59].

Rubella

Introduction

Rubella, also known as German measles, is a highly contagious viral disease that affects both children and adults. Although usually benign, infection in pregnant women, especially during the first trimester, may result in stillbirth, fetal death, or congenital rubella syndrome (CRS).

Epidemiology

The incidence of rubella has greatly reduced since the vaccine was licensed in 1969. In 2006, 58% of countries in the world already counted on rubella immunization programs, including 100% of industrialized countries [60]. However, there are still numerous records of outbreaks of the dis-

ease around the world. In Poland, in 2013, there was a rubella outbreak in adult men as a result of the restricted vaccination program established before 2004, which covered only girls of 13 years of age [61]. For similar reasons, there was an outbreak in middle-aged men in Japan in 2012/2013. Also, in 2012 in China there was an epidemic in young adults related to inadequate vaccination coverage [62].

Rubella was declared eliminated from the United States in 2004 and from the Americas in 2012, although CRS cases continue to occur, especially in countries where universal vaccination coverage is not routine [60].

Etiopathogenesis

An RNA virus of the genus Rubivirus belonging to the Togaviridae family causes rubella. The transmission occurs via nasopharyngeal droplet secretions from infected individuals who are transmitters from 5 to 7 days before and up to 7 days after exanthema onset [63].

Hospitalized patients must remain in isolation for 7 days, while children should be excluded from school activities for 7 days after the onset of rash. Children affected by CRS can remain transmissive throughout the first year of life [52].

Clinical Presentation

Rubella has an incubation period of approximately 18 days and may be preceded by nonspecific prodromal symptoms such as slight fever, eye pain, arthralgia, and sore throat.

The rash consists of discrete, pink maculopapules spreading from the face to the trunk and extremities within 24 h. The rash is pink and is not followed by desquamation (which may occur following measles).

Postauricular and suboccipital lymphadenopathy is common. Palatal enanthem (Forchheimer spots) and conjunctivitis may occur, but up to half of the patients have no symptoms at all.

Adolescents and adults are more likely to be symptomatic and have fever [60].

Box 10.4 Congenital Syndrome Rubella

The rubella virus is still a major public health problem due to teratogenic effects, and risk of miscarriage and stillbirth caused by maternal infection during pregnancy, especially in countries where immunization coverage is not universal. In maternal infection, the virus crosses the placenta and may infect the developing fetus with devastating effects when the infection occurs in the first trimester. In infected pregnant women who develop a rash within the first 12 weeks of gestation, the frequency of congenital infection is greater than 80%, decreasing thereafter, given that after the 16th week of gestation there is no risk of CRS development [64].

The manifestations of CRS may be present at birth or appear after months or years of life. It includes purpuric rash, hepatosplenomegaly, bone lesions, eye and hearing defects that can lead to blindness and deafness, cardiovascular abnormalities, and CNS disorders such as microcephaly and mental retardation. In countries without adequate vaccination coverage, CRS is the leading cause of nongenetic congenital deafness. Immune disorders are associated with the development of diabetes mellitus type 1 as a late manifestation of CRS [65].

Diagnosis and Complementary Examinations

The diagnosis of rubella cannot be established solely on clinical findings (see Box 10.5).

An elevated rubella-specific IgM antibody or a fourfold or greater rise of rubella- specific IgG antibody in paired sera obtained 2 weeks apart is generally diagnostic.

False-positive test results can be seen with other viral infections. Positive rheumatoid factor may be seen in rubella patients. Low-avidity IgG is seen with recent primary infection and high-avidity rubella IgG is associated with past infection or reinfection. PCR can detect rubella virus from nasal, throat, and urine specimens [60].

For congenital infection, the diagnostic method of choice is a viral culture from the naso-

pharynx, and after the fifth month of life a serological test may be performed [36].

Box 10.5 Laboratory diagnosis of Rubella

Diagnosis by ELISA (enzyme-linked immunosorbent assay)
Specific IgM elevation
Specific IgG elevation ≥4 times in a 2-week interval

Differential Diagnosis

The differential diagnosis is made with other causes of febrile exanthemas. Parvovirus B19 infection, HHV-6, dengue, and measles must be considered according to the age group and geographic area.

Therapeutic Approach

Treatment

The treatment for both the acquired and congenital form is symptomatic and supportive. To date there is no effective antiviral therapy available [65].

Vaccine

The rubella vaccine is highly effective and remains a key strategy for the control and elimination of rubella and CRS. Active immunization with the live attenuated virus is available. The first dose is recommended between 12 and 15 months of age and the second dose between 4 and 6 years of age [65].

The vaccine provides immunity for about 20 years, but for less time than the acquired immunity after infection, which explains increased susceptibility among women of reproductive age who were vaccinated only in infancy. The recommended additional dose of the vaccine in late adolescence as a part of the immunization program is justified [66].

Erythema Infectiosum

Epidemiology

The infection is most common in childhood and in most cases is asymptomatic. Seropositivity is

found in about half of adolescents younger than 15 years and in more than 80% of the elderly population. Distribution is global, with higher incidence in the winter and spring, and small outbreaks occur in a cyclical pattern approximately every 6 years [52, 60, 67].

Etiopathogenesis

Parvovirus B19 (PVB19) is the only parvovirus known to infect humans. This virus is responsible for a broad spectrum of clinical manifestations, erythema infectiosum – or "fifth disease" – being the main one.

The virus is transmitted through respiratory tract droplets eliminated by sick patients in the viremic phase. Vertical transmission can occur in 30% of infected pregnant women, especially in the second trimester of pregnancy, and a fetal infection can lead to miscarriage, stillbirth, severe anemia, and fetal hydrops [67]. Less commonly there may be transmission through blood transfusion or bone marrow transplantation [68].

The clinical manifestations of the PVB19 infection can be caused both by the direct effects of the virus and by immunological phenomena in response to antigen, and the symptoms also depend on the age and immunity of the host and associated comorbidities [60]. It is believed that the erythema infectiosum occurs through the formation and the deposition of immune complexes, as there is a temporal disconnect between viremia and clinical symptoms [52, 67].

PVB19 has strong tropism for erythroid precursor cells by binding to the erythrocyte P antigen, also known as globoside. This antigen can also be found in the placenta and fetal myocardium, and occasionally in megakaryocytes [67]. In patients with highly progressive disease or red blood cells of lower half-life, the infection may be responsible for transient aplastic crisis, caused by an abrupt halt of the production of erythrocytes [68].

Clinical Presentation

Erythema infectiosum is the most common clinical presentation of the PVB19 infection. See Box 10.6 for another clinical presentation, the papular-purpuric gloves and socks syndrome.

The incubation period ranges from 6 to 18 days. The viremia lasts 7–10 days after infection presenting reticulocytopenia, ceasing with the emergence of IgM anti-B19 around the 10th day. A week later, IgG antibodies arise and skin manifestations begin. It is important to note that patients with rash are no longer contagious once viremia has ceased [52, 68].

A prodrome of low fever and flu-like symptoms may be present, and 2–3 weeks later a characteristic exanthema surges, which starts with prominent macular erythema on the cheeks, sparing the nasal crest and the perioral region ("slapped cheek") (Fig. 10.18a).

The second stage occurs within 1–4 days, with erythematous papules and macules in a lace pattern mainly in the extremities and less intensely on the trunk (Fig. 10.18b, c). This exanthema is evanescent, lasts 1–3 weeks, and can reoccur with exposure to the sun or heat [52].

Arthralgia or arthritis occurs in 10% of cases of erythema infectiosum, involving small joints of the hands, wrists, ankles, and knees. They also have a self-limiting character.

In adults the rash is more subtle and systemic and articular manifestations are more prominent [68].

> **Box 10.6 Papular-Purpuric Gloves and Socks Syndrome**
> Also caused by parvovirus B19, papular-purpuric gloves and socks syndrome usually occurs in young adults, with the highest incidence in the spring, and is characterized by edema and erythema on the palms and soles, with petechiae and purpura. Patients complain of a burning and itching sensation. Erosive enanthem and petechiae on the palate, pharynx, and tongue may be present, besides mild systemic symptoms. It evolves with spontaneous resolution within 1–2 weeks and the treatment is supportive. There is evidence that the disease occurs during the viremic phase and can thus be infectious in the clinical phase. Other infectious etiologies have been reported, such as coxsackievirus B6 and HHV-6 [52].

Fig. 10.18 (**a**) Erythema on the cheeks ("slapped cheek"). (**b**, **c**) Lacy, reticulated erythematous eruption on the arms

Diagnosis and Complementary Examinations

The diagnosis is based on medical history and clinical examination. Serology may be helpful in severe or atypical cases. Enzyme immunoassay for specific IgG and IgM has high sensitivity and specificity. The detection of IgM is more clinically useful since it remains positive for up to 2–3 months after acute infection [68]. DNA hybridization techniques and PCR are particularly useful in immunocompromised patients [52].

Anemia, reticulocytopenia, thrombocytopenia, or even pancytopenia may be present. A skin biopsy is not very useful in diagnosis [68].

Differential Diagnosis

The differential diagnosis includes mainly scarlet fever, enterovirus infections, and rubella.

Therapeutic Approach

The treatment of PVB19 infection is symptomatic and supportive. There is no specific antiviral therapy and the majority of infections are self-limiting.

Nonsteroidal anti-inflammatory drugs can be used in cases of symptomatic arthropathy.

In immunocompromised patients at risk of severe complications, intravenous immunoglobulin

may be an option for the treatment of anemia, assisting in the recovery of hematopoiesis.

Whenever PBV19 infection is diagnosed, the physician must ensure that neither the patient nor his or her contacts is a member of certain vulnerable populations. In these populations, infection with PVB19 may result in devastating complications. The vulnerable populations include those with hematologic disease, immunosuppressed patients, and pregnant women [68].

Gianotti–Crosti Syndrome

Epidemiology

Gianotti–Crosti syndrome (GCS), or papular acrodermatitis of childhood, is a self-limited exanthem of acute onset with a characteristic acral distribution, which mainly affects children aged between 2 and 6 years, and more rarely young adults [69].

It is distributed worldwide and tends to predominate in spring and early summer.

Although it is an unusual dermatosis, five epidemics have been recorded, three of which occurred in Japan, with most affected persons closely associated with hepatitis B virus (HBV). The other two, with fewer affected patients, occurred in India and Italy; in the latter, all cases were associated with EBV [70].

Etiopathogenesis

Although the pathophysiologic mechanism is not fully understood, it is believed that the rash is a cutaneous response to certain immunologic triggers using a Type IV hypersensitivity reaction against antigens: viral, bacterial, or recent immunizations [69].

The syndrome is classically described in association with HBV, but today EBV is the most commonly identified agent. A list of viruses, bacteria, and vaccinations reported to be associated with GCS is given in Table 10.10 [71].

Regarding the relationship with immunizations, the incidence of SGC seems to be higher with combined vaccines or when there is a viral infection present at the time of vaccination, suggesting that

Table 10.10 Agents associated with GCS

Viral
Epstein–Barr virus
Hepatitis A, B, and C
Cytomegalovirus
HHV-6
Coxsackievirus A16, B4, and B5
Parvovirus B19
Molluscum contagiosum virus
Poxvirus
Rotavirus
Respiratory syncytial virus
Echovirus
Mumps virus
Parainfluenza virus
HIV
Bacteria
Streptococcus group A
Mycoplasma pneumonia
Borrelia burgdorferi
Bartonella henselae
Post vaccination
Influenza
MMR
Hepatitis A and B
DPT
Oral polio
BCG
Haemophilus influenzae type B

perhaps more than one immune stimulus is necessary for the development of the syndrome [72, 73].

One study showed a high prevalence of atopic dermatitis, family history of atopy, and elevated total and specific IgE levels within SGC cases, suggesting atopy as a predisposing factor [69, 74].

Clinical Presentation

The disease is characterized by the acute onset of multiple monomorphous, pink to red-brown papules or papulovesicles that may become confluent. The papules are distributed symmetrically on the face, extensor surfaces of the extremities, and buttocks (Fig. 10.19a–d). The rash is usually asymptomatic but may be pruritic.

The trunk, palms, and soles are usually spared, although some extension onto the trunk does not exclude the diagnosis.

Fig. 10.19 (**a–d**) Gianotti–Crosti syndrome. *Pink* to *red-brown* papules and papulovesicles distributed symmetrically on the extremities and buttocks

The eruptions can persist longer than 6 weeks in more than 50% of patients, and complete resolution typically takes more than 2 months.

The cutaneous manifestations can be preceded by an upper respiratory tract infection or diarrhea. The rash may be accompanied by a low-grade fever, hepatosplenomegaly, or cervical, inguinal, or axillary lymphadenopathy. Koebner's phenomenon may also be present.

Recurrence can occur rarely [69–71].

Diagnosis and Complementary Examinations

GCS is diagnosed clinically by the presence of a characteristic rash and its distribution. Lesion biopsy is usually not necessary. Histopathologic findings are nonspecific and include epidermal acanthosis, hyperkeratosis, and dermal perivascular lymphohistiocytic infiltrate, with dilatation of dermal capillaries. Investigation for hepatitis or identification of the causative agent is generally not required, but may be indicated in select cases [52, 70].

Differential Diagnosis

The GCS frame makes differential diagnosis with other viral rashes, drug eruptions, erythema multiforme, eczema herpeticum, Henoch–Schonlein purpura, papular-purpuric gloves and socks syndrome, Kawasaki disease, hand-foot-mouth disease, lichen planus, papular urticaria, and atopic dermatitis.

Therapeutic Approach

No specific treatment is necessary because of its benign nature.

Oral antihistamines and topical antipruritic may be useful for symptomatic relief.

The effectiveness of topical corticosteroids is not well established. Ribavirin has been used in prolonged or debilitating cases, but further study is needed as to its effectiveness [69, 71].

In vaccine-induced cases, there is no contraindication for subsequent doses [75].

Smallpox

Introduction

The first reports of the disease date back to 1500 BC and, until the last century, smallpox plagued humanity and accounted for more than half a million deaths per year in medieval Europe. Some authors consider it the worst epidemic worldwide to date. The last registered case of smallpox occurred in 1977, and in 1980 the disease was declared eradicated by the WHO, following a major global vaccination campaign during the 1960s–1970s [76, 77].

Etiology

Smallpox is caused by *Poxvirus variolae*, an orthopoxvirus of the Poxviridae family. It exclusively infects humans and is highly contagious and progressive, with high mortality rates.

Clinical Manifestations

Infection with the smallpox virus occurs through droplet or aerosol exposure. After an incubation period that lasts up to 14 days, the prodrome of fever and constitutional symptoms begins.

Rash appears 1–4 days after the onset of fever. The rash is characteristically centrifugal, with lesions progressing from macules to papules to umbilicated vesicles to pustules to scabs over a period of 2–3 weeks.

A person is contagious during the period when the rash is present, and infectiousness ceases after the scabs have sloughed.

The fatality rate of smallpox is approximately 25%, and severe complications such as blindness can also occur [76, 78].

Diagnosis

The suspicion is clinical and diagnosis can be made by serology, cell culture, PCR, or electron microscopy. Suspected cases should be immediately reported to the authorities [78].

Therapeutic Approach

Treatment

There is no specific treatment approved, although two drugs, tecovirimat and liposomal cidofovir, are in the testing phase, and may be useful in the event of new outbreaks of the disease [78].

Vaccine

Vaccination is still the most effective method of prevention. It is also useful for administration in the first days after exposure; it may alleviate or abort the symptoms of infection [76].

Vaccinia

Vaccinia virus (VACV) and Cowpox virus are causative agents of disease in cattle, and display serologic cross-reactivity with other members of the Poxviridae family. The bovine disease progresses with lesions in the cow's udder and can be transmitted to humans through direct contact during milking, resulting in lesions to the hands and arms [79].

In 1796 the English physician, Edward Jenner, observed that workers who came into contact with sick animals did not acquire smallpox or had a milder form of the disease. This finding led to the creation of an immunization method from the inoculation material collected from lesions, which was called "vaccination," derived from the Latin *vacca*, meaning "cow" [80, 81].

The traditional vaccine to prevent smallpox contains the VACV; it is administered via scarification of the skin and causes an infection by VACV that stimulates the immune system. Although highly effective, the replicative capacity of the virus can generate nonlocalized infection and significant adverse effects (Table 10.11) [82].

Given these considerations, the routine use of the vaccine was discontinued after eradication of the disease. This creates concern about the chances of re-emergence of smallpox from strains preserved in laboratories, since most of the population is susceptible. There is great fear about the use of the smallpox virus as a biological weapon in wars or terrorist attacks [78].

New vaccines with attenuated viruses have been studied, with a good safety profile for atopic

Table 10.11 Adverse effects of the smallpox vaccine

Progressive vaccinia: necrosis in the area of vaccine
Generalized vaccinia: scattered skin lesions, not necessarily related to the vaccination site
Eczema vaccinatum: local or generalized spread of the virus in atopic patients
Myocarditis/pericarditis
Encephalitis

patients or HIV-infected populations more prone to developing adverse effects to traditional vaccines [78, 82, 83].

Cowpox

Cowpox is a zoonotic dermatitis affecting, despite its name, mainly cats and humans. The disease is caused by the cowpox virus (CPXV), a close relative of vaccinia, smallpox (variola), and monkeypox viruses within the Orthopoxvirus genus. It is usually self-limited except in immunocompromised and atopic patients, particularly children, who may develop a severe and even fatal form of the disease [84, 85].

CPXV is transmitted to humans through contact with infected animals. It was believed initially that cattle were the natural reservoir of the virus.

Today it is considered that the true natural reservoirs are wild rodents, transmitting it to domestic animals, especially cats, which in turn transmit the disease to humans [84–86].

The vaccination for elimination of smallpox led to the suppression of cases of cowpox by cross-reactivity with the VACV. Currently, with the abandonment of the smallpox vaccination, the number of cases of cowpox in humans is increasing. The disease is more prevalent in Europe, Russia, and in the central and northern regions of Asia [85].

The virus infects humans through skin abrasions, resulting in successive lesions of macular, papular, vesicular, pustular, ulcerous, and eschar stages for 2 weeks, located mainly in the hands and face. The incubation period ranges from 7 to 12 days. Lymphadenopathy and symptoms such as myalgia, headache, and nausea are common.

The diagnosis can be done by PCR, virus isolation, serology, and electron microscopy [84].

There is no specific treatment established. Cidofovir has shown efficacy in in vitro tests and can be an option in difficult cases [85].

Milker's Nodules and Orf

Orf, or ecthyma contagiosum, is a zoonosis caused by the Orf virus, a Parapoxvirus that infects sheep and goats, and eventually humans. Transmission occurs through direct or indirect contact with infected animals or contaminated objects (see Box 10.7) [87].

After an incubation period of 3–14 days, it is manifested as skin lesions at the sites of cutaneous inoculation, usually unique, especially on the hands, arms, and forearms, although rarer locations have been described. It begins as an erythematous papule and progresses to a target lesion, evolving to exudative nodules that spontaneously regress with the formation of dry crust, until complete resolution in 6–12 weeks [52, 88].

Orf and milker's nodules, caused by the paravaccinia virus, another parapoxvirus, are clinically and histologically very similar and are differentiated by epidemiologic data. The first is endemic among sheep and goats and the second in cattle [52, 87].

Diagnosis is based on clinical history associated with contact with animals. In questionable cases it can be confirmed by histopathology, electron microscopy, serology, or PCR of lesional fluid.

Treatment is supportive, since it usually regresses spontaneously. Topical imiquimod can be used in select cases.

Shepherds, butchers, veterinarians, and farmers are occupations of risk for these diseases, and the appropriate use of gloves is the main preventive measure [52, 88].

Box 10.7 Exposure to Orf
Orf is a common occupational disease in New Zealand.

In countries with a Muslim population, it is common to find Orf unrelated to occupational exposure, but related to the slaughter of sheep in religious festivals of animal sacrifice [88].

Molluscum Contagiosum

Epidemiology

Molluscum contagiosum (MC) is a viral disease that mainly affects children, with peak incidence between 1 and 4 years of age, with no difference between boys and girls [89]. It can affect adolescents and adults, usually associated with sexual transmission. In the immunodeficient (e.g., in HIV patients), MC tends to be more severe and widespread [90, 91].

The annual incidence, including all age groups, is estimated at 2.01 in 1000 patients. In the 1–4 years age group the incidence rises to 10.2 in 1000 patients [89]. The overall reported prevalence of MC in children is between 5.1% and 11.5%.

In immunocompromised patients prevalence is between 5% and 18% and appears to be greater in warm climates. Specifically in HIV-positive patients, the prevalence increases significantly, reaching values of up to 33% in patients with CD4$^+$ T-cell counts below 100/µl [90].

MC is associated with atopic dermatitis. The lesions tend to arise in the areas of dermatitis or eczema, and children with atopic dermatitis may have a more disseminated presentation. Other MC associations are observed in children attending swimming pools, in patients with diseases that compromise immunity, or with the use of immunosuppressive drugs [36, 89, 90].

Etiopathogenesis

MC is an infection caused by the molluscum contagiosum virus (MCV), a large double-stranded DNA virus that is the sole member of the Molluscipoxvirus genus in the Poxviridae family.

Of the four identified subtypes, genotype 1 is responsible for about 90% of reported cases in the United States. Transmission occurs by direct contact with the skin of the infected person (which may be through sexual intercourse), fomites (towels, pools) or autoinoculation [36, 90, 92].

The incubation period ranges from 7 days to 3 months and the transmission occurs as long as the lesions exist. The disease has an indolent course and tends to disappear spontaneously within 2 years [90].

Clinical Presentation

MC is characterized by a typical, benign papular rash with pearly, centrally umbilicated lesions, reaching 1 mm to 1 cm, which can be found anywhere on the epidermis and more rarely on the mucous membranes (Fig. 10.20a–f).

Pruritus is also sometimes a clinical feature, and the lesions are usually painless. It more often affects the face, eyelids, axillary regions, antecubital and popliteal fossa, trunk, and extremities [36, 90, 91].

When it affects the mucosa, the most common sites are the perianal, orbital, and oral regions. Genital lesions occur in adolescents and adults (Figs. 10.21a, b and 10.22). When seen in children, it may suggest sexual abuse. The disease is rare in the palms and soles [36, 91].

Fig. 10.20 (**a–f**) Molluscum contagiosum. Pearly, centrally umbilicated lesions
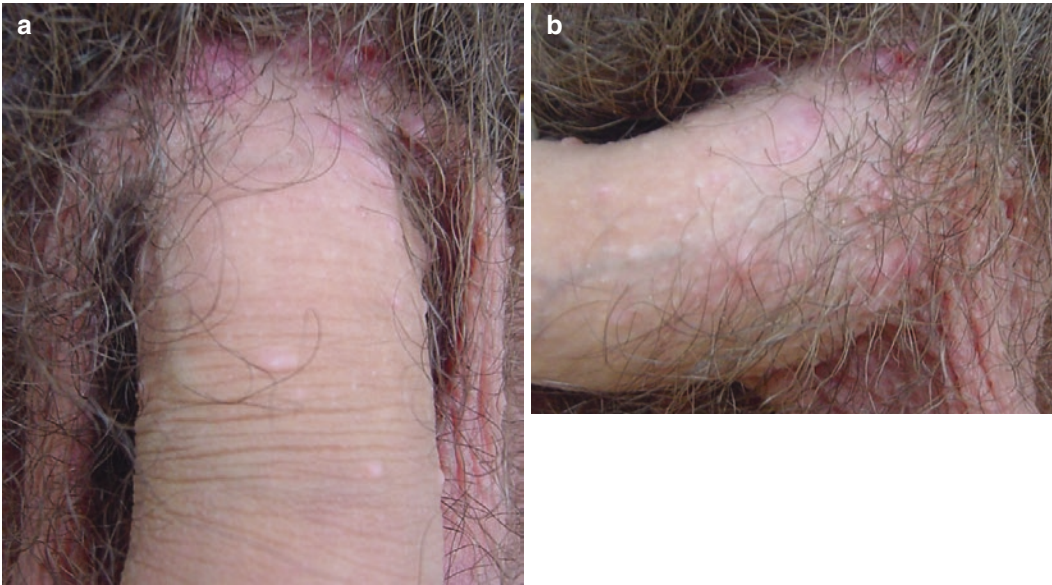
Fig. 10.21 (**a**, **b**) Molluscum contagiosum. Genital lesions in an adult

Fig. 10.22 Molluscum contagiosum. Genital lesions in an immunosuppressed girl

Diagnosis

Diagnosis is clinical, through history and evaluation of the lesions. Dermatoscopy may help to identify central umbilication and typical vascular pattern. However, biopsy with findings of Henderson–Patterson bodies, PCR to identify the MCV, or preparation of the sample on a slide with potassium hydroxide for visualization of the cells can be used for confirmatory methods [36].

Complementary Examinations

Usually not required. Investigation of immunodeficiency is suggested in atypical presentations.

Differential Diagnosis

The differential diagnosis varies according to age, immune status, and location of lesions, and is summarized in Table 10.12, adapted from Hanna et al. [92].

Therapeutic Approach

MC in healthy people is a self-limiting, relatively harmless viral skin infection. Since most lesions will resolve within months, MC can be left to heal naturally unless better evidence for the superiority of other treatment options emerges. People may seek treatment for social and aesthetic reasons and because of concerns about spreading the disease to others. Treatment is intended to speed up the healing process [93].

Pharmacologic treatment includes cantharidin, podophyllotoxin, imiquimod, potassium

Table 10.12 Differential diagnosis of MC

	General patients	Children and adolescents	Immunocompromised patients	Genital lesions
Differential diagnosis	Cysts	Nevus	Penicilliosis	Ectopic sebaceous gland
	Abscesses	Juvenile xanthogranuloma	Cryptococcosis	Vulvar lymphangioma circumscriptum
	Basal cell carcinoma	Milium	Histoplasmosis	Condyloma acuminate
	Cutaneous horn	Keratosis pilaris	Coccidioidomycosis	
	Keratoacanthoma		*Pneumocystis carinii*	
	Verruca vulgaris		Aspergillosis	

Table 10.13 Comparison between some therapeutic modalities for MC

No. of visits required	Curettage	Cantharidin	Salicylic acid	Imiquimod
1	80.6%	36.7%	53.6%	55.2%
2	16.1%	43.3%	46.4%	41.4%
3	3.2%	20.0%	0%	3.4%
Satisfaction[a]	86.7%	60.0%	32.1%	44.8%
Adverse effects	4.7%	18.6%	53.5%	23.3%
Change of treatment	7.4%	18.5%	50.0%	38.5%

Adapted from Hanna et al. [92]

[a]Patients' and parents' satisfaction

hydroxide, SA, topical retinoids, and oral cimetidine. Cantharidin requires two applications and should preferably be done by a physician. It is contraindicated for lesions on the face, genitals, and perianal region. Podophyllotoxin is applied twice daily for 3 days each week for three additional weeks and can be self-administered [36]. Topical imiquimod appears to have better results in the lesions of the face, neck, and genitals [91]. Potassium hydroxide 5% solution must be applied by parents using a tooth pick (after covering the surrounding area with petrolatum), at night, three times a week for 12 weeks or until the lesions have cleared, and washed off in the morning [92]. Retinoids also help the immune system in clearing the virus but may cause skin irritation.

Nonpharmacologic options include cryotherapy, curettage, electrodesiccation, and manual extraction. Cryotherapy is the treatment of choice for many clinicians, performed in the office with one to three sessions indicated. The procedure causes pain, which is a limiting factor for treatment in children.

Curettage is a fast and reliable treatment performed by a medical professional with local anesthesia, usually suitable for a small number of injuries. It may leave a scar and is contraindicated for genital lesions.

Nonpharmacologic options should be considered for pregnant women [90–92]. Comparison of efficacy for some modalities of treatment is described in Table 10.13.

Prevention is achieved by avoiding manipulation of the lesions, communal use of objects with contaminated persons, and direct contact with carriers of the disease.

Prions

Abbreviations used:
PrP: Prion protein
PrP^C: Cellular prion protein
PrP^Sc: Prion protein from scrapie
CJD: Creutzfeldt–Jakob disease

Prion proteins (PrP) are part of membrane cell structure, naturally present in animal cells such as neurons and keratinocytes.

The prion protein can occur in either of two structural conformations, one that is normal (but

of unknown function), designated PrP^C, and one that results in disease, called PrP^{Sc} (Sc from the word scrapie).

PrP^{Sc} are small proteinaceous infectious particles, devoid of nucleic acid, with self-replicative capacity, which are responsible for serious neurodegenerative disorders in animals and humans. The infectious protein is able to modify the spatial structure of the prion protein PrP^C, naturally present in animal cells. This new conformation of the protein is insoluble, resistant to proteases, and toxic to the affected cells [94].

The incidence of prion-related disorders is relatively stable worldwide and has been estimated at 1 case per 1 million inhabitants annually. Most common forms are sporadic, accounting for 85% of all cases, whereas approximately 10–15% of instances are inherited forms and less than 2% are acquired forms [95].

In animals prions cause scrapie, the prototype disease of this group that affects sheep and goats, and bovine spongiform encephalopathy (mad cow disease). Human prion diseases include Creutzfeldt–Jakob disease (CJD), Gerstmann-Straussler-Scheinker syndrome (GSS), kuru, fatal familial insomnia (FFI), PrP cerebral amyloid angiopathy, and variably protease-sensitive prionopathy [96]. The explanation of these diseases is beyond the scope of this book.

Transmission occurs through direct contact with brain-derived materials and affected corneas, such as the transmission of kuru through cannibalism among tribes in New Guinea and CJD by eating contaminated beef [97].

Iatrogenic transmission can occur through surgical manipulation with contaminated instruments. Prions are able to adhere to metal surfaces and are extremely resistant to conventional decontamination methods. Bovine products used in health, such as cell culture media, catgut, and collagen implants used in dermatology, present an active risk of disease transmission [94, 98].

The presence of native PrP protein in skin keratinocytes makes the skin a possible point of entry, by scarifying or inoculating infected materials. Skin affected by psoriasis, eczema, or chronic ulcerations hyperexpresses PrP, becoming a target for prion infection [94].

Emerging Viruses

Abbreviations used:
Dengue virus:DENV
Zika virus: ZIKV
Chikungunya virus: CHIKV
Ebola virus: EBOV

Emerging viral diseases are a constant challenge in medicine. Tourism, economic globalization, immigration, and climate change are factors that contribute to the spread of infectious diseases.

New pathogens are being identified, the geographic distribution of diseases is constantly changing, and new clinical syndromes caused by known pathogens are being discovered [99].

This section addresses Ebola, dengue, chikungunya, and Zika. The main aspects of these diseases are listed in Table 10.14.

Table 10.14 Emerging viruses: main features

	Transmission	Cutaneous manifestations	Noncutaneous manifestations	Diagnosis	Endemic areas
Ebola	Direct contact with bodily fluids	Nonspecific macules and papules	Flu-like symptoms and hemorrhages	RT–PCR[a], antigen-capture ELISA[b], antibody-capture ELISA, and virus isolation	Guinea, Liberia, Sierra Leone (last endemic area)
		Pinpoint papules around hair roots and proximal extremities			
		Diffuse erythroderma			
		In darker skin: fine scaling			
		Petechiae, purpura, ecchymoses, and hematomas, particularly around needle or puncture sites			

Table 10.14 (continued)

	Transmission	Cutaneous manifestations	Noncutaneous manifestations	Diagnosis	Endemic areas
Dengue	Bite of infected mosquitoes of the genus *Aedes*	Classic dengue: maculopapular rash that mainly affects the trunk – describe as "islands of white in a sea of red." This may be pruritic and heals with desquamation	Classic dengue: fever for 2–5 days, severe headache, intense myalgia, arthralgia, retro-orbital pain	Rapid test; RT–PCR if <7 days after symptom onset (or NS1 antigen ELISA); antibody testing if ≥4 days after symptom onset or if molecular testing is negative: IgM[c] ELISA and PRNT[d]	Tropical and subtropical areas of Asia, Americas, Africa
		Discrete hemorrhagic manifestations	Hemorrhagic dengue: more severe course, vomiting, weakness, hemodynamic instability		
		Hemorrhagic dengue: facial flushing, circumoral cyanosis, petequias, equimoses, and vibices in different topography			
Zika	Bite of infected mosquitoes of the genus *Aedes*; sexual contact; vertical; (saliva, semen, breast milk, urine?)	Blanchable macules and papules that start on the face or trunk and extends to extremities. The eruption may be pruritic and heals with desquamation. Typically spares the palms and soles	Fever, arthritis or arthralgia, and conjunctivitis	RT–PCR in urine; antibody testing if ≥4 days after symptom onset or if molecular testing is negative: IgM, ELISA, and PRNT	South and Central America, Caribbean, Pacific Islands
		Mild hemorrhagic manifestations			
Chikungunya	Bite of infected mosquitoes of the genus *Aedes*	Morbilliform rash, which can become confluent	Symmetric polyarthralgia, most frequently in the hands, wrists, and ankles	RT–PCR if <7 days after symptom onset; antibody testing if ≥4 days after symptom onset or if molecular testing is negative: IgM, ELISA, and PRNT	Asia, Africa, Latin America, Caribbean, Florida, Puerto Rico, US Virgin Islands
		In male: aphthous-like ulcers in the scrotal region, associated with scrotal erythema and pain and swelling of the scrotum and groin	High grade fever		
		Xerosis of skin with scaling, desquamation of palms	Severe malaise		
		Acute intertrigo-like lesions			
		Lymphedema in an acral distribution			
		Nasal hyperpigmentation			
		Vesiculobullous lesions			
		Itching, generalized urticaria			
		Purpuric patches, rarely			
		Exacerbation of a patient's underlying dermatoses			

[a]*RT–PCR* reverse transcriptase–polymerase chain reaction
[b]*ELISA* enzyme-linked immunosorbent assay
[c]*IgM* immunoglobulin M
[d]*PRNT* plaque reduction neutralization test

Ebola

The Ebola virus disease (EVD), formerly known as Ebola hemorrhagic fever, is caused by the viruses of the Ebolavirus genus. Ebola was first discovered in 1976 near the Ebola River in the Democratic Republic of Congo. Since then sporadic outbreaks have occurred in Central Africa, and a major epidemic occurred in 2014, affecting several countries in Africa.

The disease is transmitted through direct contact with the blood or bodily fluids. It is initially presents with sudden nonspecific flu-like symptoms, and nonspecific cutaneous manifestations appear 4–5 days after the fever. Bleeding is frequently observed, causing petechiae, purpura, and ecchymoses. The clinical course is severe and lasts about 14–21 days, and mortality rates reach 90% [55].

Dengue, chikungunya, and Zika virus are transmitted by the bite of the same vector, the *Aedes* mosquitoes, mainly *Aedes aegypti*, an anthropophilic species that is an aggressive daytime biter well adapted to urban environments. This enabled the occurrence of simultaneous outbreaks of these diseases in tropical countries such as Brazil, other countries in Latin America, Asia, and Oceania.

These viruses cause quite similar febrile clinical syndromes, making differential diagnosis difficult [100, 101].

Furthermore, the emergence of new complications such as congenital Zika syndrome, and the occurrence of disease in travelers around the world, is making this a public health concern of global proportions [102].

Dengue

Dengue virus (DENV) belongs to the family of Flaviviridae, and DENV complex is composed of five serotypes. Infections are transmitted by the bite of infected mosquitoes of the genus *Aedes*, primarily *Aedes aegypti*. Dengue is the most prevalent mosquito-borne viral disease and an important cause of morbidity and mortality in tropical and subtropical regions. Clinical manifestations of the disease vary and include asymptomatic infection, classic dengue, dengue hemorrhagic fever (DHF), and dengue shock syndrome. Most dengue infections are asymptomatic and a mild disease resembles any acute febrile illness, with high-grade fever, malaise, and retro-orbital pain [103].

Patients should to avoid aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs).

Chikungunya

Chikungunya is an acute febrile illness caused by the Chikungunya virus (CHIKV) of the Togaviridae family, and also transmitted by *Aedes* mosquitoes. The illness was initially discovered in Africa in 1952 and is endemic to many countries in Asia, Africa, Latin America, and the Caribbean [55, 104].

The name chikungunya, which is used to describe both the virus and the disease, is derived from a Swahili or Makonde word *kun qunwala*, meaning "to become contorted" or "that which bends up." The most characteristic symptom of chikungunya is severe and symmetric polyarthralgia (see Box 10.8). Although most symptoms resolve, some patients have joint pain that can continue for years and can be so severe that they adopt a bent or stooping posture [105].

Box 10.8 Key points for Chikungunya clinical presentation
Severe joint pain
   High fever, headaches, photophobia
   Maculopapular rash in legs and arms that lasts for 2–3 days

Zika

Zika virus (ZIKV) is a single-stranded RNA virus in the genus Flavivirus, which originated in the Zika forest in Uganda and was discovered in a rhesus monkey in 1947. The disease now has "explosive" pandemic potential, with outbreaks in Africa, Southeast Asia, the Pacific Islands, and the Americas. Since Brazil reported Zika virus in May 2015, infections have occurred in at least 20 countries in the Americas [106].

The transmission of ZIKV has been associated with several *Aedes* mosquito species, notably *A. aegypti* and *A. albopictus*. However, other factors may contribute to the rapid spread of the virus. ZIKV is detectable in blood, urine, semen, breast milk, and saliva from patients and can persist in urine for several months after clinical resolution of the disease [107].

Although transmission through blood transfusion has not been reported, it is likely to occur. Spread of the virus through sexual contact has been reported, and viral RNA has been detected in semen 62 days after symptom onset. Men who have had a diagnosis of ZIKV disease must wait at least 6 months after symptom onset before attempting conception [55].

Several reports demonstrated vertical transmission of ZIKV to the fetus in pregnant women. Intrauterine infections are associated with the occurrence of microcephaly, other congenital malformations, and miscarriages, which is being called "Zika congenital syndrome" [102, 108, 109]. The actual magnitude of these complications cannot yet be estimated. There is also an association with ZIKV infection and postinfectious GBS under investigation [106].

On February 1, 2016, the WHO declared that the rapid spread of ZIKV in the Americas and the increasing reports of cases of congenital malformations and neurologic complications in ZIKV-affected areas constitute a "public health emergency of international concern." Box 10.9 shows the main clinical aspects of ZIKV.

> **Box 10.9 Key points for ZIKV clinical presentation**
> Mild symptoms, conjunctivitis usually present
>   ZIKV present in breast milk, semen, saliva, urine
>   Guillain–Barré syndrome
>   Congenital Zika syndrome

Diagnosis

Diagnosis of dengue, chikungunya, and Zika is based on anamnesis, symptoms, and test results (see Box 10.10 and Fig. 10.23 with CDC algorithm).

Zika can be difficult to differentiate from dengue and chikungunya infections. Compared with dengue, Zika virus infection has a mild to moderate clinical picture and conjunctivitis is common.

Dengue usually presents with retro-orbital pain, not associated with conjunctivitis, and a more severe muscle pain.

Chikungunya presents with higher fever and more intense joint pain [55].

ZIKV is more frequently detected in urine and saliva than in blood using ZIKV RT–PCR tests.

Patients exhibit the highest concentrations of ZIKV in saliva at disease onset while in urine; ZIKV possibly remains detectable for longer periods [111].

A point-of-care (POC) assay to specifically detect IgM and IgG antibodies to ZIKV and a multiplex POC assay to simultaneously detect antibodies to ZIKV, DENV, and CHIKV are in development. The multiplex POC assay could be of particular utility in areas where these arboviruses cocirculate [112]. Rapid tests for dengue are available and can be used in field settings.

> **Box 10.10 Tips for differential diagnosis**
>
> | | |
> |---|---|
> | Dengue | Retro-orbital pain |
> | Chikungunya | Polyarthralgia |
> | Zika | Conjunctivitis |

Tiered algorithm for arbovirus detection for suspected cases of chikungunya, dengue, or Zika (Testing only performed if patient symptomatic and travel history indicates travel to affected area.)

Molecular testing[1] (<7days after symptom onset)

Antibody testing[1] (≥4days after symptom onset)

RT-PCR/NS1 dengue — (Real time) PCR-Zika virus — (Real time) PCR-chikungunya virus

IgM dengue — IgM Zika virus — IgM chikungunya virus

Positive: dengue virus Confirmed | Negative: Perform antibody testing[2]

Positive: Zika virus Confirmed | Negative: Perform antibody testing[2]

Positive: chikungunya virus Confirmed | Negative: Perform antibody testing[2]

Positive: Presumptive dengue virus[3] | Negative

Positive: Presumptive Zika virus[3] | Negative

Positive: Presumptive chikungunya virus | Negative

PRNT[4]   PRNT[4]   PRNT

- [1]Due to extensive cross-reactivity in flavivirus serological assays, for samples collected <7 days post illness onset, molecular detection should be performed first.
- [2]Perform if sample ≥4 days after symptom onset.
- [3]Extensive cross-reactivity would be expected in samples from DENV/ZIKV circulation areas. A positive IgM assay with either antigen should be confirmed by using PRNT against both ZIKV and DENV as well as any other flavivirus (eg. SLEV, ZIKV, WNV, etc.) that might be found in that geographic area (including travel areas).
- [4]PRNT should include any flavivirus (eg. SLEV, ZIKV, WNV, etc.) that might be found in that geographic area (including travel areas).

Fig. 10.23 CDC algorithm for suspected cases of chikungunya, dengue, or Zika [110]

Therapeutic Approach

Treatment is nonspecific and supportive.

Aspirin and other NSAIDs should be avoided until dengue is excluded.

A dengue quadrivalent vaccine was approved recently in Brazil, Mexico, and the Philippines.

There is no vaccine for CHIKV or ZIKV.

The prevention or reduction of transmission of DENV, ZIKV, and CHIKV is completely dependent on the control of mosquito vectors and limiting person-mosquito contact.

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Suggested Literature

www.cdc.gov.
www.who.int.

Fungal Infections

11

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Key Points Summary

- Superficial fungal infections are caused by pathogenic fungi and are limited to the human hair, nails, epidermis, and mucosa
- Superficial fungal infections are caused by dermatophytes, which require keratin for growth, *Candida* sp., which infect warm areas, and various yeasts and lipophilic fungi of the genus *Malassezia*
- Subcutaneous mycoses include a heterogeneous group of infections that often result from direct penetration of the fungus into the skin through trauma
- Systemic mycosis is characterized by infections caused by truly pathogenic fungi as well as those produced by fungi with small intrinsic pathogenicity, enhanced by immunocompromised hosts
- Subcutaneous and systemic fungal infections are caused by numerous fungi, which invade the skin, mucosal sites, and CNS
- Fungal infections can have various clinical presentations
- Diagnosis of mycoses is made from mycologic studies, direct examination, stains, and isolation and identification of the fungi

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Superficial Mycosis

Superficial mycoses are fungal infections of the skin, hairs, and nails that invade only the stratum corneum and the most superficial layers of the skin, and include dermatophytoses, tinea versicolor, candidiasis, tinea nigra, and piedras (white and black).

Dermatophytosis

Dermatophytosis, also known as tinea, is a superficial fungal infection of the stratum corneum, nails, and hair caused by dermatophytes, which includes three genera: *Trichophyton* sp., *Microsporum* sp., *and Epidermophyton* sp.

Epidemiology

Of the 40 different species of dermatophytes, about 30 have been known to cause human infections. They are distributed worldwide, although dermatophytosis is more prevalent in hot, humid tropical and subtropical climates.

Dermatophyte infections can be transmitted from person to person through fomites, especially among family members; from animals to humans; and acquired from soil [1, 2]. The most important sources of fungal infection are the bath, showers in fitness studios, changing rooms at public pools, and mats in sports facilities. Dermatophytosis infection can be either direct (rarely, via skin contact from one person to another) or indirect (most common, from walking barefoot on surfaces that have been contaminated with infectious material from the skin, floors, rugs, etc.). Children and adolescents are frequently affected by zoophilic dermatophytes, whose sources are house pets, especially cats and rodents, and less often, farm animals, or outbreaks among the family or at a school/daycare [2].

Members of the same species can produce quite different clinical pictures, including age-group selectivity: *Tricophyton tonsurans*, for example, can produce tinea capitis in children and tinea corporis in adults.

Trichophyton rubrum is the most common cause of tinea pedis, nail infection, tinea cruris, and tinea corporis worldwide, once it targets structures of the stratum corneum of the epidermis and the nail keratin. However, *T. rubrum* only rarely causes thricophytosis [1, 2].

Etiopathogenesis

Dermatophytes can be separated into three groups based on their habitat. Anthropophilic dermatophytes are restricted to human hosts, producing mild chronic inflammation, and are the main cause of chronic infections. *T. rubrum*, *Trichophyton concentricum*, *Trichophyton schoenleinii*, *T. tonsurans*, and *Trichophyton mentagrophytes* var. *interdigitale* are the most involved species. Zoophilic dermatophytes (*Microsporum canis*, *Trichophyton verruco-*sum, *Trichophyton mentagrophytes* var. *menta-grophytes*), the main reservoirs of which are pets, livestock, and horses, usually cause infection with marked inflammatory reaction in humans [3]. *Microsporum gypseum* is the most common geophilic dermatophyte. It usually causes tinea manus and has been reported in infections after contact with soil, for example, when gardening [2].

In addition, reactions to a dermatophyte infection may range from mild to severe as a consequence of the host's reactions to the metabolic products of the fungus, the virulence of the infecting strain or species, the anatomic location of the infection, and local environmental factors [4].

The dermatophytes target the hard, firm cyto-keratin found in the skin, hair, and nails in order to proliferate in the stratum corneum. They destroy the complex protein keratin via keratinase and adhere to the epithelial tissue of the host by mannan glycoproteins in the cell wall of the fungus. The nutritive medium for the fungus and the host–pathogen interaction are also important factors, among others [2].

Dermatophytes are restricted to the stratum corneum because keratinocytes act as a physical barrier against them and are also involved in cutaneous immune reactions. They express pattern recognition receptors, which promote the release of various proinflammatory cytokines and chemotactic factors and cause inflammatory reactions, such as redness and swelling. To prevent fungal infection, keratinocytes also release antimicrobial peptides. Chemotactic factors recruit inflammatory phagocytes, which engulf dermatophytes, release cytokines, and produce reactive oxygen species that cause damage in proteins, lipids, and DNA, thereby destroying the phagocytosed pathogens. Local fungal infections induce the production of circulating antibodies and activate T lymphocytes, leading to various localized or generalized inflammatory reactions called "id reactions" [5].

Table 11.1 shows main fungal species of dermatophytosis.

Table 11.1 Commonest etiologic agents causing dermatophytosis

Diagnosis	Etiologic agents
Tinea barbae	*Trichophyton verrucosum*, *T. mentagrophytes*
Tinea capitis	*T. tonsurans*, *Microsporum canis*, *M. audouinii*, *T. verrucosum*, *T. violaceum*, *T. soudanense*
Tinea corporis	*T. rubrum*, *M. canis*, *T. tonsurans*
Tinea cruris	*Epidermophyton floccosum*, *T. rubrum*, *T. interdigitale*
Tinea incognito	Potentially any cutaneous dermatophytosis that has been inappropriately treated with topical steroid
Tinea manuum	*T. rubrum*, *T. mentagrophytes*
Tinea pedis	*T. rubrum*, *T. interdigitale*, *E. floccosum*
Onychomycosis	*E. floccosum*, *T. interdigitale*, *T. rubrum*, *T. verrucosum*

Fig. 11.1 Tinea corporis in a diabetic patient with eruptive xanthomas

Clinical Presentation

Dermatophytoses are classified according to the affected area of the body in tinea corporis, tinea pedis, tinea cruris, tinea capitis, and tinea unguium (dermatophyte onychomycosis) [1].

Tinea Corporis

Ringworm of the body, usually involving the trunk, shoulders, or limbs, and occasionally the face (excluding the bearded area), may be caused by any dermatophyte. The infection has a broad range of manifestations, with lesions varying in size, degree of inflammation, and depth of involvement. In classic ringworm erythemato-squamous, scaly plaques grow centrifugally (Fig. 11.1). They are initially flat, scaly spots that then develop a raised border that extends out at varying rates in all directions. The advancing, scaly border may have red, raised papules or vesicles, while the central area turns brown or hypopigmented and becomes less scaly as the active border progresses outward, forming an annular, irregular plaque (Figs. 11.2 and 11.3). Lesions can be single or multiple, asymptomatic, or mildly itchy, and can self-resolve or enlarge, covering large areas of the body [1, 6] (Figs. 11.4 and 11.5).

Fig. 11.2 Tinea corporis (axilla) in a patient with eruptive xanthomas

Fig. 11.3 Tinea corporis on the back

Fig. 11.4 Extensive tinea corporis (*T. rubrum*) in a pregnant patient (*back*)
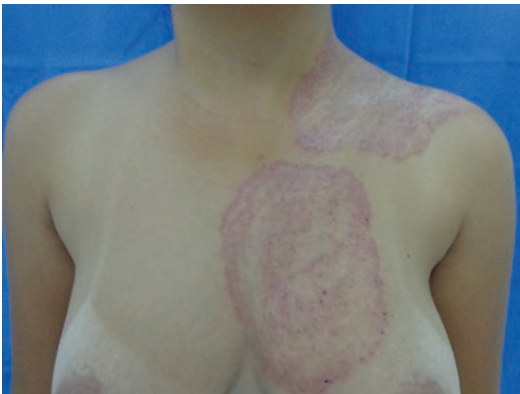
Fig. 11.5 Extensive tinea corporis (*T. rubrum*) in a pregnant patient

Fig. 11.6 Tinea circinata on the back (*T. tonsurans*)

Fig. 11.7 Tinea faciei in a malnourished patient

Tinea circinata (Fig. 11.6) is a specific form of tinea corporis frequently caused by *T. tonsurans* that has a peculiar ring-like morphology. It is difficult to differentiate from tinea imbricata (tokelau), which is caused by the slow-growing dermatophyte *Trichophyton concentricum* and occurs in Southeast Asia (Vietnam, Polynesia), Africa, and South America [6].

Tinea faciei appears as erythematous, centrifugally growing, discretely scaly patches with prominent borders, frequently on the cheeks, but also on the eyelids and the submandibular region (Fig. 11.7). It can be mildly or even nonpruritic. In children, zoophilic dermatophytes are the primary pathogens [6].

Tinea Cruris ("Jock Itch")

Infection of the groin, perianal, and perineal areas, and occasionally the upper thighs, is usually seen in adult men. *T. rubrum* and *Epidermophyton floccosum* are the most frequent etiologic agents. Lesions are erythematous to tawny brown and covered with thin, dry scales. They are usually bilateral and often asymmetric, extending down the sides of the inner thigh and exhibiting a raised, sharply marginated border that is frequently studded with small vesicles [4]. The promoting factor is the presence of a warm, moist environment, such as excessive sweating or wearing wet clothes. Itching becomes worse as moisture gathers and macerates the intertriginous area [1].

Tinea of the Hand

The palmar and interdigital areas of the hand are usually involved in tinea manus, most frequently presenting as unilateral diffuse hyperkeratosis with accentuation of the flexural creases. Most infections are caused by *T. rubrum* [4].

Tinea Pedis

Tinea pedis is the dermatophyte infection of the foot, also called athlete's foot. Predisposing factors are warmth and sweating. Locker room floors and communal baths are important sources for this infection. Most cases occur in late childhood and young adulthood [1].

The soles and toe webs are most frequently involved in tinea pedis. The most common clinical manifestation is the intertriginous form, which presents with maceration, peeling, and fissuring, mainly in the spaces between the fourth and fifth toes. Another common presentation is the chronic, squamous, hyperkeratotic type in which fine silvery scales cover pinkish skin of the soles, heels, and sides of the foot (moccasin foot) (Fig. 11.8). An acute inflammatory condition (dyshidrotic type), characterized by the formation of vesicles, pustules, and sometimes bullae, is most frequently caused by *Trichophyton mentagrophytes*. The more chronic agents of tinea pedis are *T. rubrum*, *T. mentagrophytes* var. *interdigitale*, and *E. floccosum* [1, 6].

Tinea Capitis

Tinea capitis, an infection commonly involving the scalp, is usually caused by members of the genera *Microsporum* and *Trichophyton*. It is the most relevant dermatophyte infection in children between 3 and 8 years of age. The infection is related to poverty, large family size, and crowded living conditions. It originates from contact with a pet or an infected person, by direct contact, or from contaminated clothing. Untreated asymptomatic scalp infections in schoolchildren and adults are important contributing factors to disease transmission and reinfection [1, 6].

The infection may range from mild, almost subclinical, with slight erythema and a few patchy areas of scaling with dull gray hair stumps (Figs. 11.9 and 11.10), to a highly inflammatory

Fig. 11.9 Tinea capitis in a preschool child (*M. canis*)

Fig. 11.8 Tinea pedis, "moccasin foot" (*T. rubrum*)
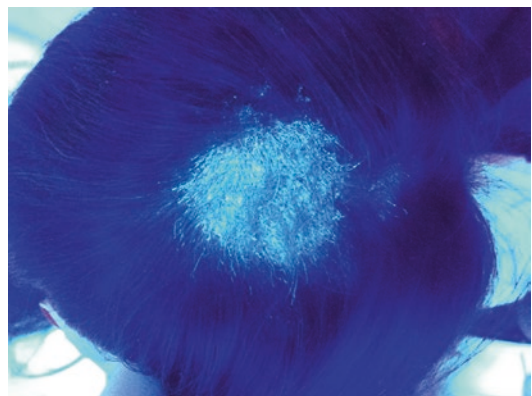
Fig. 11.10 Tinea capitis (*M. canis*): bright green Wood's light fluorescence

reaction with folliculitis, kerion formation, and extensive areas of scarring and alopecia, sometimes accompanied by fever, malaise, and regional lymphadenopathy. Dermatophytes show either an endothrix or an ectothrix pattern of hair root involvement. In endothrix infections by *T. tonsurans*, *Trichophyton violaceum*, *Trichophyton soudanense*, and *T. verrucosum*, (arthro)spores and mycelia may be microscopically detected inside the hair shaft, without any destruction of the cuticle. In ectothrix infections by *M. canis*, *Microsporum audouinii*, and *Trichophyton interdigitale* (zoophilic strains), spores and hyphae aggregate in a cuff-like fashion outside the hair shaft [6].

The current predominant cause of tinea capitis in most of North, Central, and South America is *T. tonsurans* (endothrix) [4]. In Brazil, *M. canis* (ectothrix) is also an important etiologic agent.

Tinea Barbae

Tinea barbae, an infection of the bearded area, may be mild and superficial or a severe inflammatory pustular folliculitis (resembling fungal kerions seen in tinea capitis). The latter form is more commonly caused by the zoophilic dermatophytes *T. verrucosum* and *T. mentagrophytes* var. *mentagrophytes* [4]. Bacterial folliculitis and inflammation secondary to ingrown hairs may be complications of tinea. The deep follicular infection has an appearance similar to that of bacterial folliculitis but is slower to evolve and usually restricted to one area of the beard.

Tinea Incognito

Tinea incognito, or tinea atypica, is a term used to describe a tinea infection modified by topical steroids. It is caused by prolonged use of topical steroids, sometimes prescribed as a result of incorrect diagnosis. Topical steroids decrease inflammation and give the false impression that the rash is improving while the fungus continues to thrive secondary to cortisone-induced immunologic changes. Clinically, lesions initially resemble eczema-like and psoriasis-like dermatoses as well as lupus erythematosus. Tinea incognito is usually seen on the groin, face, dorsal aspect of the hands, and trunk [1, 6].

Tinea Unguium or Onychomycosis

Invasion of the nail plate by a dermatophyte is referred to as tinea unguium; onychomycosis is a word often used as a general term for a nail fungal infection.

Onychomycosis may involve a single nail or all nails. Toenails are seven times more likely to be affected than fingernails. The first and fifth toenails are the most commonly affected, often following an episode of tinea pedis. Fingernail infection is, in contrast, usually associated with tinea corporis or capitis, and is often unilateral [7].

Four types of onychomycosis are recognized. Distal and lateral subungual onychomycosis (DSO) is the most common form of onychomycosis. It clinically appears as hyperkeratosis of undersurface of distal nail plate and bed; onycholysis and dyschromias (Fig. 11.11). It is associated with one hand–two feet syndrome and tinea pedis is often present. Proximal (white) subungual onychomycosis, a relatively uncommon subtype, occurs when organisms invade the nail unit via the proximal nail fold and migrate distally. The clinical presentation includes subungual hyperkeratosis, proximal

Fig. 11.11 Tinea pedis and onychomycosis: hyperkeratosis of undersurface of distal nail plate and bed

onycholysis, leukonychia, and destruction of the proximal nail plate. It is common in acquired immune deficiency syndrome (AIDS) patients and is considered an early clinical marker of human immunodeficiency virus (HIV) infection. White superficial onychomycosis is less common than DSO and occurs when certain fungi invade the superficial layers of the nail plate directly. It can be recognized by the presence of well-delineated opaque "white islands" on the external nail plate, which coalesce and spread as the disease progresses. The nail becomes rough, soft, and crumbly. It usually affects children and the most common etiologic agent is *T. mentagrophytes*. Total dystrophic onychomycosis is used to describe end-stage nail disease may be the end result of any of the main patterns of onychomycosis. The entire nail unit becomes thick and dystrophic [8].

Dermatophytid or Id Reactions

Dermatophytid is a hyperergic reaction to dermatophyte components as a result of antimycotic treatment of extensive tinea. Id reactions present clinically as symmetric dyshidrotic eruptions on hands and feet, or as nodular and multiform eruption, predominantly on the extremities. It can be falsely misdiagnosed as adverse drug reaction or intolerance to antimycotic agents, but lesions slowly resolve, even if the drug is continued [6].

Box 11.1 Specific Forms of Dermatophytosis
Majocchi's granuloma: a form of inflammatory tinea usually caused by *T. rubrum* and originally reported as occurring on the lower leg of women who shave, but is also seen at other sites on men and children. The primary lesion is a pruritic, scaly, follicular papulopustule or inflammatory nodule. Subsequently deep infiltration of mycelia along hair follicles results in their rupture, leading to a granulomatous follicle-associated inflammatory reaction. Intracutaneous and subcutaneous granulomatous nodules arise. It particularly affects immunosuppressed patients. Lesions have

necrotic areas containing fungal elements which are surrounded by epithelioid cells, giant cells, lymphocytes, and polymorphonuclear leukocytes [1, 6].

Two feet–one hand syndrome: a dermatophyte infection of both feet and one of the palms. Nail infection of the hands and feet can also be present. It usually occurs in men and *T. rubrum* is the causative organism in most cases [1].

T. rubrum syndrome: represents a chronic and generalized dermatophytosis, also referred as chronic dermatophytosis syndrome, generalized chronically persistent rubrophytia, tinea corporis generalisata, and dry-type *T. rubrum* infection. *T. rubrum* syndrome is characterized by infection of at least four body sites: feet (plantar), hands (palmar), nails, as well as one other site. The inguinal region is not affected. Other diagnostic criteria are microscopic fungal detection from all four sites and cultural detection of *T. rubrum* from at least three out of four sites. Predisposing factors includes Down syndrome, HIV infection, diabetes mellitus, and corticosteroid treatment [6].

Complementary Examinations

The most important test for the diagnosis of dermatophyte infection is direct visualization under microscopy of the branching hyphae in keratinized material [1].

Scale from the active border of a lesion (collected with a scalpel blade), pulled-out hairs from the affected area or, in the case of nails, subungual debris should be placed on the center of a microscope slide and covered with a coverslip. Then potassium hydroxide, 5–20% solution, should be applied at the edge of the coverslip. Under microscopy, dermatophytes are identified as septated, tube-like structures called hyphae and mycelia [1].

Fungal cultures are slow and expensive and are usually not needed in cases where the same oral and topical agents are effective against all of

the dermatophytes. However, it can be useful in cases of tinea capitis and onychomycosis, when long-term oral therapy is considered. Fungal cultures are grown on Sabouraud's glucose medium and usually take 7–14 days to be declared positive; culture must be held 21 days to be declared negative [6].

A Wood's lamp (filtered UV light) can be used to visualize hairs infected with *Microsporum* species, which fluoresce in a greenish color in a dark room (Fig. 11.10). *Microsporum* is a very common cause of tinea capitis in many parts of the world, including Brazil. Favus, a rare chronic form of tinea capitis caused by *Trichophyton schoenleinii*, will fluoresce a pale green with examination under Wood's light. A Wood's lamp can be also used to differentiate tinea and intertrigo from erythrasma, which fluoresces a brilliant coral red color [9].

Diagnosis

> **Box 11.2 Diagnosis of Dermatophyte Infection**
> Dermatophyte infections can be readily diagnosed based on the history, physical examination, and potassium hydroxide (KOH) microscopy. Diagnosis occasionally requires Wood's lamp examination and fungal culture or histopathologic examination.

Differential Diagnosis

TINEA CORPORIS – psoriasis vulgaris; impetigo; atopic dermatitis; contact dermatitis; erythema multiforme; and granuloma annulare [6].

TINEA FACIEI – contact dermatitis; atopic dermatitis; lupus erythematosus; granuloma faciale; herpes zoster; impetigo; perioral dermatitis; polymorphous light eruption; psoriasis vulgaris; rosacea; sarcoidosis; and seborrheic dermatitis [6].

TINEA CRURIS – intertrigo and erythrasma [1].

TINEA MANNUM – palmar psoriasis; atopic hand dermatitis; and contact dermatitis.

TINEA PEDIS – Interdigital: erythrasma; and interdigital candidiasis [6]. Moccasin-type: atopic dermatitis; plantar psoriasis; and pitted keratolysis.

[6] Dyshidrotic type: dyshidrotic eczema; contact dermatitis; impetigo; juvenile plantar dermatosis; and keratolysis exfoliative [6].

TINEA CAPITIS – alopecia areata; bacterial abscess of the hairy scalp; impetigo; furuncle/carbuncle; seborrheic dermatitis; pityriasis amiantacea; pityriasis capillitia; psoriasis; syphilis; and trichotillomania [6].

TINEA UNGUIUM – psoriasis; lichen planus; yellow nail syndrome; and alopecia areata [7].

Therapeutic Approach

Topical Treatment

Topical antifungals are effective in the treatment of tinea and they should generally be applied twice daily in the involved area for 2–4 weeks, including 1 week after lesions have disappeared. Topical antimycotics that can be used against dermatophytes include imidazoles (such as bifonazole 1%, clotrimazole 1%, econazole 1%, miconazole 2%, and sertaconazole), ciclopirox olamine 1%, terbinafine 1%, amorolfine 0.025% (nail lacquer 5%), and tolnaftate 1%. Available presentations are cream, lotion, spray, powder, and solution nail lacquer. Combination of an antimycotic and a corticosteroid is effective in treating inflammatory forms of tinea pedis, but should not be used for longer than 14 days [1, 10] (Table 11.2).

Systemic Treatment

Both systemic antifungal and topical agents should be used together. Oral treatment is imperative for tinea capitis, extensive tinea corporis, onychomycosis (indications for oral treatment include proximal subungual onychomycosis, at least 50% of the nail plate affected, involvement of the nail matrix or multiple nails, and no response to topical treatment after 6 months), and chronic tinea pedis.

Tinea Corporis

Tinea corporis is treated by 150–200 mg of fluconazole once weekly for 2–4 weeks, by 200 mg itraconazole daily for 7 days, or by 250 mg terbinafine daily for 1 week. Deep inflammatory lesions require 1–3 or more months of oral therapy [1].

Table 11.2 Tinea treatments

	Topical treatment	Systemic treatment
Tinea pedis	Bifonazole 1× daily for 2–4 weeks	Terbinafine 250 mg daily for 1–2 weeks
	Clotrimazole 2–3× daily for 2–4 weeks	
	Econazole 2× daily for 2–4 weeks	
Tinea corporis	Miconazole 1–2× daily for 2–4 weeks	Itraconazole 200 mg daily for 1 week
	Sertaconazole 1× daily for 2–4 weeks	
Tinea manuum	Ciclopirox olamine + terbinafine 1× daily for 2–4 weeks	Fluconazole 150–200 mg once weekly for 2–6 weeks
	Amorolfine 2× daily for 2–4 weeks	
	Tolnaftate 2× daily for 2–4 weeks	
Tinea cruris	Available presentations: cream, lotion, spray, powder, gel	
Tinea capitis	Ketoconazole 2% shampoo 2–3× weekly for 2–4 weeks	Terbinafine 250 mg daily for 4–6 weeks in adults
		Children according to weight:10–20 kg, 62.5 mg/day; 20–40 kg, 125 mg/day; >40 kg, 250 mg/day
	Selenium sulfide 1% shampoo 2–3× weekly for 2–4 weeks	Griseofulvin 1,000 mg daily for 6–12 weeks in adults and 20–25 mg/kg/day (max 1 g) daily in children
	Povidone–iodine 2.5% shampoo 2–3× weekly for 2–4 weeks	Fluconazole 6 mg/kg per day for 3–6 weeks or once weekly for 6–12 weeks
	Ciclopirox 1% shampoo 2–3× weekly for 2–4 weeks	Itraconazole 5 mg/kg (maximum 400 mg) 1× daily for 2–4 weeks in adults and 3–5 mg/kg/day 1× daily for 2–4 weeks in children
Tinea barbae		Terbinafine 250 mg 1× daily for 4 weeks
		Itraconazole 200 mg 1× daily for 2 weeks
Onychomycosis	Amorolfine 5% lacquer 1–2× weekly for 6–12 months	Terbinafine 250 mg 1× daily for 12 weeks for toenails or for 6 weeks for fingernails
		Or
	Ciclopirox 8% lacquer 1× daily for 24 weeks on fingernails and for 48 weeks on toenails	Intermittent treatment option: terbinafine 250 mg 1× daily for 5–14 days, followed by 250 mg weekly until clinical cure is achieved
		Or
	Keratolysis with 20% or 40% urea cream applied under occlusion	Terbinafine 500 mg 1× daily for 1 week every month for 3 consecutive months
	Miscellaneous: surgical nail removal, phonophoresis, manual and electrical nail abrasion, acid etching, microporation, ultrasonography, laser nail ablation, iontophoresis, lasers (Nd:YAG short pulse and Q switch 1,064 nm and the diode 870, 930, and 980 nm), photodynamic therapy, topical germicidal ultraviolet C light58	Itraconazole 100 mg 2× daily for 3 months
		Or
		Intermittent treatment option: Itraconazole 200 mg 2× daily for 1 week, followed by an interval of 3 weeks for 3 months
		Fluconazole 150 mg 1× weekly (one single dose) for 3–6 months for fingernails and 6–12 months for toenails
		Or
		Fluconazole 300 mg (up to 450 mg) single weekly dose for 3–6 months for fingernails and 6–12 months for toenails

Tinea Pedis

Terbinafine, 250 mg tablet daily for 2 weeks; itraconazole, 200 mg twice daily for 1 week; or fluconazole, 150 mg once weekly for 2–6 weeks [1, 10].

Tinea Capitis

Griseofulvin is the current drug of choice in children, in dosages of 20–25 mg/kg/day for 6–12 weeks, especially in cases of *M. canis*. The recommended daily dose in adults is 1,000 mg per day divided in two doses.

In 2007, terbinafine became the second drug approved by the US Food and Drug Administration to treat tinea capitis in children [9]. Safety, efficacy, and cost data favor terbinafine for treatment of *T. tonsurans* infections [1]. General guidelines for tinea capitis are treatment for 4–6 weeks, with dosage determined by body weight: 62.5 mg/day in patients weighing from 10 to 20 kg, 125 mg/day from 20 to 40 kg, and 250 mg/day over 40 kg [1]. There is also some evidence that itraconazole and fluconazole are effective and safe for tinea capitis caused by *M. canis* and *Trichophyton* species [11].

Prednisone (1–2 mg/kg/day) for 1 or 2 weeks in addition to griseofulvin and adjuvant topical therapy can be used in patients with kerion [9].

Tinea Unguium; Onychomycosis

The two main systemic drugs indicated for the treatment of onychomycosis are terbinafine and itraconazole. Terbinafine, given as 250 mg daily for 6 weeks for fingernails and for 12–16 weeks for toenails, should be considered as first-line treatment because of fewer drug interactions and because it is superior both in vivo and in vitro for dermatophyte onychomycosis. Regular monitoring of liver function tests after 4–6 weeks of oral treatment is recommended [7].

Itraconazole is less active than terbinafine against dermatophytes. It is given as 200 mg/day (12 weeks for toenails, 6 weeks for fingernails) or as a monthly pulsed treatment of 400 mg/day for 1 week of each month (two pulses for fingernails, three pulses for toenails) [7].

Fluconazole seems to be less effective than either itraconazole or terbinafine, although it remains a potential third-line treatment. Fluconazole is inexpensive, has good compliance rates, has few drug interactions, and also is highly effective against both dermatophytes and *Candida* species [7].

Griseofulvin is authorized in children but is no longer suggested as first-line therapy because of long treatment duration and poor efficacy. If there are no contraindications, terbinafine, itraconazole, or fluconazole with dose adjustment according to weight and age can be used to treat onychomycosis [7] (Table 11.2).

Pityriasis Versicolor

Pityriasis versicolor (PV), or tinea versicolor, is a common superficial fungal infection of the skin caused by *Malassezia* yeasts, that presents as flaky round or oval macular elements, usually located in the upper aspects of the trunk, neck, and arms (Fig. 11.12) [1, 12, 13].

Epidemiology

The prevalence of PV varies by geography and age, The disease is thus more frequent among people living in a hot and humid climate in tropical parts of the world. It can occur at any age but is more common in adolescents and young adults, and is equally distributed between men and women [1, 12, 13].

The etiology is multifactorial and genetic susceptibility seems to play a role. Other recognized risk factors are malnutrition, oral contraceptives,

Fig. 11.12 Pityriasis versicolor lesions on the upper trunk

immune suppression, hyperhidrosis, and use of oil or greasy skincare products as well as topical corticosteroids [13].

Etiopathogenesis

PV is caused by various yeasts and dimorphic lipophilic fungi of the genus *Malassezia*, previously known as *Pityrosporum* sp. The most important species are *Malassezia globosa*, *Malassezia sympodialis*, and *M. furfur* [12].

The organism is part of normal skin microflora. It lives within the stratum corneum and hair follicles in areas of high sebaceous activity where it feeds off free fatty acids and triglycerides [1].

Malassezia pathogenicity mechanisms and their relation to disease and clinical manifestations remain to be elucidated. However, it is known that the yeasts become pathogenic when the immune balance is disturbed.

When the predisposing factors are present, the yeast converts from the budding form to its mycelial form, which leads to the formation of tinea versicolor [1].

Dicarboxylic acids produced by the fungus, i.e., azelaic acid, can have a cytotoxic effect on melanocytes and prevent dopa tyrosinase reaction, causing a reduction in number, size, and aggregation of melanosomes in melanocytes and surrounding keratinocytes. This is the cause of hypopigmented lesions, which are more apparent as unaffected skin tans. Inflammatory skin response can be seen as red or hyperpigmented macules, another presentation of the disease [1].

Clinical Presentation

PV presents as multiple, circular, or oval macules which may be hypochromic or hyperchromic (versicolor), covered with fine scales. The spectrum of colors of the lesions includes: red to fawn-colored macules, patches, or follicular papules; hypopigmented lesions, which generally occurs in dark-skinned individuals; and tan to dark-brown macules and patches. Mixed cases can be found, especially in the axillae, groin, and submammary folds [1, 12].

Lesions initially are small but rapidly enlarge, forming large, irregular patches. The most affected area is the upper trunk, but it can spread to the upper arms, neck, and abdomen. Facial lesions, especially in the forehead, are more common in children. The lesions are generally asymptomatic but can be pruritic [1, 12]. Box 11.3 shows the Malassezioses.

Box 11.3 Malassezioses

Malassezioses are a group of diseases related to *Malassezia* spp. infection with increasing importance in the medical scenario.

- Seborrheic dermatitis is a benign, chronic, multifactorial erythematosquamous dermatosis. It is related to hormonal, environmental, psychological, immunologic, and infectious (*Malassezia* spp.) factors. Clinically its most common manifestation is scalp flaking ("dandruff"), but it can also affect the nasolabial folds, eyebrows, glabella, the retroauricular region, and the central area of the chest. It usually asymptomatic, but mild pruritus can be reported. *Malassezia* spp. are found in most cases, especially *Malassezia restricta*, *M. globosa*, and *M. furfur*. The use of topical and systemic antifungals decreases the signs and symptoms [12, 14].

- Folliculitis due to *Malassezia* is a superficial infection of the pilosebaceous unit. It is an opportunistic infection related to *M. globosa*, *M. furfur*, and *Malassezia pachydermatis* that affects young adults. Clinically it presents as pustules localized around the follicles without comedones in the trunk, the shoulders, and exceptionally, the face, and must be distinguished from acne. Histologically, there is follicular dilatation and inflammatory infiltrate with yeast colonization [12].

- Onychomycosis due to the *Malassezia* spp. is a rare and controversial dermatomycosis. *M. globosa* and *M. furfur* infection have been reported, and some authors consider it a true infection, whereas others believe that the yeasts

found are only carriers. Clinically it is a distal subungual onychomycosis that is similar to dermatophytic infection [12].

- *Malassezia* yeasts have also been associated with many diseases, including atopic dermatitis, psoriasis, blepharoconjunctivitis, dacryocystitis, confluent and reticulated papillomatosis (Gougerot–Carteaud), systemic infections, endocarditis, and bloodstream infection [12, 14].

Complementary Examinations

Skin scraping should be examined by light microscopy: *Malassezia* cells reproducing by unipolar budding and hyphae in a meatballs and spaghetti pattern are typical when *Malassezia* is more than just a colonizer [13].

Wood's light (filtered UV light) may be used as a diagnostic tool. Under Wood's light, PV lesions present a typical yellow-green fluorescence, which can help to visualize the extent of the affected skin areas. However, a negative Wood's light examination does not exclude PV as not all *Malassezia* species fluoresce [13].

Diagnosis

Box 11.4 Diagnosis of Pityriasis Versicolor
Clinical findings, "Zireli sign", fungal microscopy. Wood's light can help to visualize the extent of the affected skin areas.

Differential Diagnosis

Pityriasis alba, hypochromic solar dermatitis, pityriasis rosea, vitiligo, seborrheic dermatitis, secondary syphilis, and postlesional melanodermas [1, 12].

Therapeutic Approach

Malassezia yeasts could be susceptible to a wide variety of antifungal agents. However, relapse rates remain high [14, 15].

Topical agents are based on an antifungal and/or a keratinolytic effect and will usually be sufficient, whereas systemic treatment alone or in combination with topical treatment should be reserved for severe cases or infections refractory to topical treatment [13].

Ketoconazole is the most extensively studied antifungal therapy. Ketoconazole 2% shampoo can be used once daily for 5 days (level of evidence A I) and ketoconazole 2% cream one to two times daily for 2 weeks (level of evidence B I). Based on limited data, other effective options are zinc pyrithione shampoo, selenium disulfide shampoo, and propylene glycol in aqueous solution [13] (Table 11.3).

The three most recommended oral antifungals are ketoconazole, itraconazole, and fluconazole. Oral ketoconazole (once the first line of systemic treatment) is no longer approved for superficial fungal infections in Canada, the United States,

Table 11.3 Treatment of pityriasis versicolor

Topical treatment	Systemic treatment
Antifungal agents	
Ketoconazole 2% shampoo 1× daily for 5 days	Fluconazole 300 mg weekly for 2–4 weeks
Ketoconazole 2% cream one to two times daily for 2 weeks	Fluconazole single dose of 400 mg
Ciclopirox olamine 1.5%	Itraconazole 200 mg daily for 1 week or 100 mg daily for 2 weeks
Shampoo two times weekly for 2 weeks	Itraconazole single dose of 400 mg
Miconazole cream twice daily	Pramiconazole 200 mg/day over 2–3 days
Clotrimazole cream twice daily for 2 weeks	
Terbinafine cream or gel twice daily for 1 week	
Miscellaneous products	
Selenium sulfide 2.5% shampoo once daily for 3 days followed by the same procedure one week later	
Zinc pyrithione 1% shampoo two to three times weekly	
Propylene glycol 50% in water twice daily for 2 weeks	

and Europe, owing to the risk of its associated hepatotoxic side effects. A systematic review and meta-analysis of clinical studies indicated that itraconazole and fluconazole seemed equally effective for the treatment of PV. Hald et al. has recommended fluconazole as a preferred agent, based on its lower potential for drug interaction and side effects (Table 11.3). Pramiconazole, a new oral agent introduced since 2005, has also been described as effective, but may be associated with many adverse side effects [12, 13, 15].

Few studies have focused on maintenance therapy. Itraconazole 200 mg twice daily 1 day per month for 6 months and topical treatment with selenium disulfide (2 years of treatment every third month) have shown satisfactory results. Prophylactic daily treatment with ketoconazole 2% shampoo for up to 3 days in the beginning of the summer season has also been recommended [13]. Finally, it should be noted that it may take several months to regain a normal skin appearance despite successful treatment, especially for hypopigmented lesions.

The primary treatment objective is the mycologic cure rate. In addition, patients should be strongly advised that because relapses are common they should avoid predisposing factors [12, 13].

White Piedra

White piedra is a chronic, asymptomatic, superficial mycosis of the hair shafts, causing concretions or soft, whitish nodules [12].

Epidemiology

Most cases occur in tropical and temperate regions, and are observed in young men and women and in children.

The most important predisposing factors are humidity, hyperhidrosis, and poor personal hygiene. Long hair, excessive use of hair oil, and cultural practices such as tying of a veil, especially when done on wet hair, have also been reported [12, 16].

The most affected hairs are those of the scalp, but it can also occur in the pubis, axillae and, more rarely, beard, moustache, eyebrows, and eyelashes [12].

Etiopathogenesis

It is caused by yeast-like organisms of the genus *Trichosporon*, mainly *Trichosporon cutaneum*, *Trichosporon ovoide* and *Trichosporon inkin* [12].

Clinical Presentation

White piedra presents as asymptomatic, small, soft concretions that initially can only be palpated. A 1- to 3-mm, visible, whitish concretion with well-defined borders then develops. A single shaft may have several concretions. The nodules can be white, tan, or even reddish-green, and do not fluoresce on Wood's light examination. On microscopy, they are arranged circumferentially around the hair shaft and can easily be detached. The affected hairs can become brittle and break at points of cuticular invasion and swelling [12, 17].

Complementary Examinations

Microscopic examination reveals masses of septate hyphae with arthrospores, blastoconidia, and arthroconidia. Cultural techniques are not usually required to diagnose piedra.

Diagnosis

> **Box 11.5 Diagnosis of White Piedra**
> Whitish, small, soft concretions on the hair shafts and direct microscopic examination with masses of septate hyphae with arthrospores, blastoconidia, and arthroconidia.

Differential Diagnosis

Pediculosis (nits), trichorrexis nodosa, monilethrix, and hair caps [12].

Therapeutic Approach

Piedra is best treated by shaving or clipping the hair and, subsequently, topical antifungal azole lotions/shampoos must be used. If the disease is disseminated, the whole affected area should be shaved. The use of 2% ketoconazole shampoo is extremely practical and effective, and oral antifungals such as terbinafine and itraconazole have been used successfully in resistant cases [12, 16].

Black Piedra

Black piedra is a superficial mycosis that usually affects the hair shafts of the scalp in the form of black, hard concretions or mycotic nodules [12].

Epidemiology

Most cases occur in tropical regions with high rainfall in young men and women and in children. Humidity and poor personal hygiene are the most important predisposing factors [12].

Etiopathology

It is caused by *Piedraia hortae*, a pigmented fungus [12].

Clinical Presentation

Black piedra presents as asymptomatic, brown or black, limited, spindle-shaped, hard concretions, most frequently located on the hairs of the scalp, consisting of dark-colored thick hyphae. The stone-like nodules are tightly adherent to the hair shaft [12, 17].

Complementary Examinations

Potassium hydroxide preparation of a crushed nodule from an infected hair: when crushed, the dark-colored, branching, thick (4–8 μm) septate pigmented hyphae can be seen, usually with large oval asci, and ascospores. Cultural techniques are not usually required to diagnose piedra except for confirming the diagnosis.

Diagnosis

> **Box 11.6 Diagnosis of Black Piedra**
> Asymptomatic, brown or black, limited, spindle-shaped hard concretions, most frequently located on the hair shaft. Microscopy: dark-colored, branching, thick, septate pigmented hyphae, large oval asci, and ascospores.

Differential Diagnosis

Pediculosis (nits), trichorrexis nodosa, monilethrix, and hair caps [12].

Therapeutic Approach

Treatment of black piedra includes clipping infected hairs and applying topical antifungal or keratolytic [12].

Tinea Nigra

Tinea nigra is a rare superficial dermatomycosis caused by a pigmented yeast *Hortae werneckii* [12].

Epidemiology

Most cases occur in the coastal areas of tropical and subtropical regions. It occurs predominantly in children and young men and women [12].

Etiopathogenesis

Tinea nigra is caused by *H. werneckii*, a dematiaceous fungus that grows in an aqueous medium and adapts easily to hypersalinity. Hyperhidrosis of the hands and feet is the most important predisposing factor. In fact, this is considered to be indispensable for the development of the fungal infection [12].

Clinical Presentation

This dermatomycosis is an asymptomatic, chronic condition that presents as a gradually enlarging, hyperpigmented, irregular, circumscribed

patches or spots, ranging in color from tan to dark brown or black, covered with fine scales; that is, it can be confused with melanocytic lesions. It usually affects the palms, generally unilaterally, but can also manifest on the dorsal aspects of the hands, soles, arms, legs, neck, and trunk [12].

Complementary Examinations
Direct microscopic examination, which shows multiple dark, septate hyphae and yeast cells, and culture on Sabouraud agar medium confirm the diagnosis. Dermoscopy is useful to differentiate tinea nigra from nevi and melanoma. The characteristic dermatoscopic pattern of tinea nigra is an almost reticulated patch formed by pigmented spicules that do not respect the dermatoglyphic lines. Biopsy specimens are not necessary for diagnosis [12, 18].

Diagnosis

> **Box 11.7 Diagnosis of Tinea Nigra**
> Hyperpigmented, irregular, circumscribed patches or spots, ranging in color from tan to dark brown or black, covered with fine scales. Direct microscopy: multiple dark, septate hyphae and yeast cells. Culture on Sabouraud agar medium confirms the diagnosis. Dermoscopy is useful to differentiate tinea nigra from nevi and melanoma.

Differential Diagnosis
The differential diagnosis is made with melanocytic lesions and exogenous pigmentation.

Therapeutic Approach
Treatment is based on the control of hyperhidrosis. Keratolytics, such as 3% salicylic acid, Whitfield ointment, and topical antifungals, such as bifonazole, clotrimazole, ketoconazole, terbinafine, and ciclopirox olamine may be used. Oral itraconazole (100 mg/day) is also effective [12].

Candidiasis

Candidiasis is a fungal infection caused by any of the species from the genera *Candida*, which includes about 150 different species of yeast, amongst which *Candida albicans* is the most common causative species, accounting for up to 80% of cases [19, 20].

Epidemiology
Candida, a yeast-like fungus, is a common organism present in the reproductive and gastrointestinal mucosa. *Candida* species are commensal and colonize the skin and mucosal surfaces of healthy humans, and may cause infections that range from non-life-threatening mucocutaneous illnesses to invasive conditions, which may involve severe infection to destruction of vital organs infection. Critically ill or otherwise immunocompromised patients are more prone to develop both superficial and life-threatening *Candida* infections. *Candida* infections also constitute the most common fungal infections in AIDS patients, predominantly causing oropharyngeal candidiasis. Candidiasis is also more frequent in prematurity, exposure to broad-spectrum antibiotics, diabetics, and older patients [19, 21].

Etiopathogenesis
Of the possible 150 different species of the genus *Candida*, few have been known to cause human infections; with *C. albicans* being the most pathogenic. The few other species found to be pathogenic to humans include *Candida krusei*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Candida lusitaniae*, *Candida dubliniensis*, *Candida kefyr*, *Candida guilliermondii*, and *Candida stellatoidea* [19].

The main transmission mechanism is through endogenous candidemia, whereby *Candida* species that constitute the microbiota of various anatomic sites under conditions of host weakness behave as opportunistic pathogens. Another mechanism for transmission is exogenous, occurring mainly through the hands of health

professionals who care for patients or healthcare materials such as contaminated catheters and intravenous solution [21].

Clinical Presentation

Infections caused by *Candida* are broad-spectrum, ranging from superficially oral thrush or vaginitis to systemic infection, commonly referred as candidemia, which are mostly life threatening. Depending on the site, signs and symptoms of infection can vary from septicemia (systemic) to itching, burning, pain and a white curd-like substance at the site of the infection/lesion (mucosal). Mucosal lesions can be of the pseudomembranous (white patches) or erythematous (reddened area) type [22].

Oral Candidiasis

Oral candidiasis (candidosis) presents in a variety of clinical guises and may affect one or more mucosal surfaces. Pseudomembranous candidiasis, commonly called thrush, presents clinically as confluent whitish-yellow creamy plaques on the surface of the oral mucosa and tongue that can be readily removed to reveal an area of inflammation in the underlying membrane. This form is most common in immunocompromised individuals, particularly with HIV infections and AIDS. In fact, more than 90% of HIV-positive persons will acquire at least one episode of oropharyngeal candidiasis during progression to AIDS, while esophageal candidiasis is considered an AIDS-defining illness. Erythematous, hyperplastic, angular cheilitis and glossitis are other clinical presentations of candidiasis [22].

Vulvovaginal Candidiasis and Candidal Balanitis

About 75% of all women experience at least one episode of vulvovaginal candidiasis (VVC) in their lifetime. The clinical symptoms of VVC are nonspecific and can be associated with a variety of other vaginal diseases, such as bacterial vaginosis, trichomoniasis, and gonorrhea. The most common clinical manifestations are vulvar pruritus and burning accompanied by vaginal soreness and irritation, leading to dyspareunia and dysuria.

The discharge is usually white, thick, and odorless. Vulvar and vaginal erythema, edema and fissures are also commonly found [23].

Proposed host-related risk factors include pregnancy, hormone replacement, uncontrolled diabetes mellitus, immunosuppression, antibiotic and glucocorticoid use, and genetic predispositions [23].

Candidal balanitis is particularly seen after intercourse, following antibiotic therapy, and in diabetes, for which it may be the presenting symptom. The typical case is mild, with a dry, glazed, erythematous surface to the glans penis and on the undersurface of the prepuce. In addition, very small, irregular, eroded papules and a dispersed vesicular eruption may be present, often with plaques of white, cheese-like matter. Itchy and scaly erythematous lesions may also be present on the penile and scrotal skin [24].

Intertriginous Candida Infection

Cutaneous candidiasis predominantly affects intertriginous areas, i.e., groin, abdominal skin folds, inframammary skin, but also interdigital spaces (interdigital candidiasis). It is typically characterized by erythematous (bright red to purple-red), erosive, dry, scaly lesions, but sometimes also oozing as well as macerated especially in intertriginous candidiasis lesions with prominent borders. Pustules are also typical of cutaneous candidiasis. The risk of infection is increased by humidity, poor hygiene, obesity, pregnancy, and diabetes. For more informations, to see chapter 41 and figure 41.27.

Candidal Onychomycosis

Candidal paronychia is the most common type of candidal onychomycosis, and its incidence is higher among individuals whose nails are constantly exposed to moisture. It is characterized by *Candida* invasion of the nail plate after having affected the soft tissue around the nail. Surrounding soft tissues demonstrate inflammation and will be red and edematous. If the nail matrix is infected, transverse depressions, known as "Beau's lines," can appear. Progressive infec-

tion results in a rough, irregular, convex, and finally dystrophic nail [25].

Chronic Mucocutaneous Candidiasis

Chronic mucocutaneous candidiasis is a syndrome resulting from such fungal proliferation in which the skin and nails as well as oral, esophageal, and genital mucosa become chronically infected. It is not a single disease entity but represents the final common clinical pathway resulting when one or more of the complex defense mechanisms restricting *C. albicans* proliferation is defective. The major clinical symptoms of patients with this disorder are the disfiguring lesions of the skin and nails, the dysphagia resulting from ulcerative and inflammatory lesions of the buccal cavity and esophagus, and the symptoms that may be secondary to associated disorders such as endocrinopathies.

Complementary Examinations

Direct microscopic examination is a cost-effective, rapid method for the diagnosis of candidiasis and demonstrates rounded yeast cells with single or multiple budding, pseudohyphae, and/or blastoconidia. *Candida* species readily grow on Sabouraud dextrose agar (SDA) medium, the most commonly used medium for the isolation of the yeast. Aerobic culturing on SDA at approximately 37°C for 24–48 h results in the formation of convex cream colonies. Differentiation between strains of *Candida* may be required in refractory lesions or in immunocompromised individuals. While some media may differentiate between several species through macroscopic colony characteristics, complete differentiation between different strains of *Candida* requires immunohistochemical techniques. In addition, antifungal sensitivity testing may be useful in resistant

lesions to determine susceptibility and to direct definitive antifungal therapy [26].

Diagnosis

Therapeutic Approach

Oral Candidiasis

Nystatin 100,000–400,000 IU/ml and 4–6 ml four to five times a day for 14 days should be administered. Successful treatment depends on the time of contact with the oral mucosa for at least 2 min. Therapeutic options are oral fluconazole 200 mg in the first day and 100 mg/day for 7–14 days, itraconazole, and voriconazole; the other options are considered only in patients unresponsive or intolerant to fluconazole [27].

Vaginal Candidiasis

There is evidence that topically applied azole therapy over a period of 3–7 days is more effective than nystatin. The options for topical therapy are clotrimazole vaginal tablets, 500 mg/day; miconazole 2% cream, 5 g/day; miconazole, 100 mg, 200 mg, or 1,200 mg (single dose), vaginal suppositories; nystatin, 100,000 IU vaginal tablets (10–14 days). Oral triazoles are a safe and efficient alternative to topical therapy: fluconazole 150 mg once a day, single dose, and itraconazole 200 mg once a day for 3 days or 400 mg single dose are commonly used [27].

Intertriginous Candida Infection

Nystatin, clotrimazole, ketoconazole, or oxiconazole may be used for *Candida* infections. Topical treatments are applied twice daily until the rash resolves. Fluconazole, 100–200 mg daily for 7 days, is used for resistant fungal infections.

Candidal Onychomycosis

Topical antifungal has been used for the treatment of mild to moderate candidal onychomycosis. For instance, amorolfine, which exhibits fungicidal activity against *C. albicans*, is available as a 5% lacquer and is applied to the affected nail once or twice weekly for 6–12 months.

Box 11.8 Diagnosis of Candidiasis

Clinical presentation and direct microscopic examination (rounded yeast cells with single or multiple budding, pseudohyphae, and/or blastoconidia). Culture: SDA.

Itraconazole (200 mg per day or as pulse therapy 400 mg per day for 1 week each month) should be considered the first-line treatment for *Candida* onychomycosis, since it is more cost-effective and more likely to be associated with greater compliance. Fluconazole can be used as an alternative if there are contraindications to using itraconazole [28].

Systemic Candidiasis

For the treatment of invasive candidiasis, amphotericin B and its formulations, fluconazole, voriconazole, and echinocandins are the available drugs. The recommended doses for non-neutropenic patients are: caspofungin, loading dose 70 mg, then 50 mg daily; fluconazole, 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily; lipid formulation amphotericin B, 3–5 mg/kg daily; voriconazole 400 mg (6 mg/kg) twice daily for two doses, then 200 mg (3 mg/kg) twice daily [29].

Subcutaneous and Systemic Mycoses

Subcutaneous mycoses include a heterogeneous group of infections that often result from direct penetration of the fungus into the skin through trauma. Systemic mycosis is characterized by infections caused by truly pathogenic fungi and also those produced by fungi with small intrinsic pathogenicity, enhanced by immunocompromised hosts. In the majority of cases, the respiratory tract may be the first site of entry; fungi then usually spread hematogenously to other organs.

Sporotrichosis

Sporotrichosis is the most reported subcutaneous mycosis worldwide [30] and is characterized by the subacute and chronic evolution of cutaneous or subcutaneous nodular lesions.

Epidemiology

This fungal dermatosis is caused by the thermally dimorphic fungus *Sporothrix schenckii*, which is found throughout the world as a saprobic organism, particularly in subtropical and tropical areas [31].

It develops mainly through penetration of the fungus into the dermis after wounds or abrasion of the skin produced by infected materials or contact with cattle and feed; or inhalation of spores through the respiratory tract [31].

No age, gender, or race is spared of this infection as its occurrence depends upon the fungus in the environment and the portal of entry. The preponderance of males in most reported cases is attributed more to their higher exposure risk than gender susceptibility [30].

Animals are not a significant source of infection in humans. However, cats have been found to be important vehicle in dissemination of *S. schenckii* in a long-lasting epidemic of sporotrichosis in Brazil, diagnosed by isolation of *S. schenckii* from different types of samples, both from humans and felines, indicating the emergence of another risk factor in the epidemiologic setting [30].

Etiopathogenesis

S. schenckii complex comprises more than six species of closely related dimorphic fungi, already identified: *S. schenckii*, *Sporothrix brasiliensis*, *Sporothrix globosa*, *Sporothrix mexicana*, *Sporothrix albicans*, and *Sporothrix luriei* (rare) [32].

Clinical Presentation

Sporotrichosis is classified as a primary cutaneous disease, with three different clinical presentations: lymphocutaneous, fixed, and disseminated. Extracutaneous disease includes osteoarticular, which is the most common, pulmonary, mucosal, or systemic [32].

Lymphocutaneous

It is the most common variety and accounts for 70–80% of the cases of cutaneous sporotrichosis. The extremities are affected most frequently. The sporotrichotic chancre, a noduloulcerative lesion, at inoculation site and a string of similar nodules along the proximal lymphatics, with or without transient satellite adenopathy, characterizes this
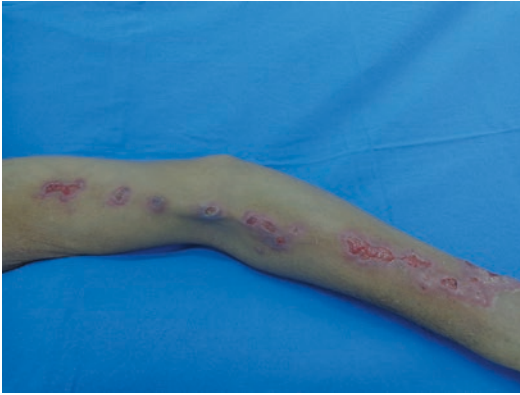
Fig. 11.13 Sporotrichosis: lymphocutaneous form

Fig. 11.14 Sporotrichosis: fixed cutaneous form

form (Fig. 11.13). These secondary lesions that appear along the lymphatics have varied morphology of erythematous papules, plaques, or nodules, having smooth or warty surface, and may soften and ulcerate, discharging seropurulent material. They are mostly asymptomatic and have an indolent clinical course similar to that of the primary lesions [30].

Fixed Cutaneous

In some patients there is no lymphatic dissemination during the course of the disease, with the lesion remaining confined to the site of initial inoculation. This is known as fixed cutaneous sporotrichosis. This form occurs less commonly, and facial involvement occurs more frequently than in the lymphocutaneous variety. The lesions may be papular, plaque-like, nodular, verrucous, or ulcerated, and can also occur in the neck, trunk, or legs (Fig. 11.14).

Often they become chronic because there is no tendency for spontaneous resolution [30, 33].

In children, the fixed cutaneous form is more common than in adults, accounting for more than 30% of cases [32].

Disseminated

Disseminated or multifocal *S. schenckii* infection is rare. When it does occur it is usually in the context of cellular immunodeficiency. The clinical picture is multiple subcutaneous nodules, gummatous lesions, or abscesses, affecting at least two anatomic sites, which develop through hematogenous dissemination or autoinoculation. The disease can affect the skin, lungs, meninges, and osteoarticular system [31, 33].

Extracutaneous

The extracutaneous form is even rarer and is difficult to diagnose because of the absence of skin lesions. It is caused by inhalation of spores or by hematogenic dissemination from a deep inoculation site and usually occurs in the setting of immunosuppression such as alcoholism, diabetes, and AIDS. Although sinusitis, pulmonary, ocular, or central nervous system (CNS) disease, meningitis, and endophthalmitis are the usual manifestations, osteoarticular sporotrichosis remains the most common systemic manifestation, found in up to 80% of cases of extracutaneous disease [30, 33].

Complementary Examinations
Culture

Pus, synovial fluid, sputum, blood, or tissue fragment is suitable for culture. Incubation is performed at 25°C using SDA or potato dextrose agar. Colonies usually appear within 3–5 days and are characterized by pigmented, membranous, radiated growth, and the characteristic microscopic features of sympodial conidia resembling daisy flowers (Fig. 11.15) [32, 33].

Histologic Examination

Histopathologic findings are generally nonspecific because the fungus, most of the time, cannot be visualized in the granulomas (even in silver-stained histologic sections), especially when suppuration is missing. This fungal derma-
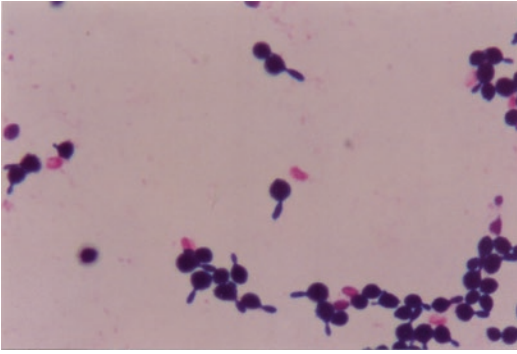
Fig. 11.15 Yeast form of *Sporotrix schenkii* (Courtesy of Prof. Sydney Hartz, Alves/UFSM)

tosis produces granulomatous inflammation associated with epithelial hyperplasia and a histiocytic plasma cell infiltrate. Asteroid corpuscles can be seen and constitute the fungal element, surrounded by an eosinophilic material resulting from protein deposition that is responsible for the antigen and antibody reaction [33].

Sporotrichin Reaction
This is a skin test antigen with *Sporothrix* obtained by culture and a positive reaction suggests the diagnosis of sporotrichosis. In cases of disseminated disease in which there is anergy, the cutaneous sporotrichin test is not useful [33].

Serologic Tests
Serologic studies to detect antibody titers can also be done, but low sensitivity and cross-reactions must be considered [32].

Diagnosis

> **Box 11.9 Diagnosis of Sporotrichosis**
> Correlation of clinical, epidemiological, and laboratory data. Fungal culture provides a definitive diagnosis of this mycosis.

Differential Diagnosis
Lymphocutaneous form: cat scratch disease (bartonellosis), lymphangitis, bacterial infec-

tion, leishmaniasis, tularemia, nocardiosis, typical mycobacterial infection. *Fixed cutaneous form:* syphilis, leishmaniasis, paracoccidioidomycosis, chromoblastomycosis, cutaneous tuberculosis, leprosy, squamous cell carcinoma.

Therapeutic Approach
Potassium Iodide
Potassium iodide is still considered first-line treatment in many third-world countries because of its low cost, efficacy, and safety profile. Its mechanism of action remains unknown and it is used in cutaneous forms, especially for fixed cases. The dosage is 3–6 g daily for 3–6 months, increasing from 5 to 40 drops three times a day or the maximally tolerated dose. Treatment should be continued until at least 4 weeks after apparent clinical cure. The mechanism of action is unknown [32, 33].

Side effects include gastric intolerance, edema, rash, and erythema nodosum. Thyroid suppression or thyrotoxicosis must be avoided, detected, and treated [32].

Itraconazole
The most effective triazole by far is itraconazole, for both lymphocutaneous disease (responses 100% at 6 months' treatment) and osteoarticular disease (about 85–100% response in several series) [35].

It is administered at a dose of 100–200 mg/day for 3–6 months. For children, the recommended dose is 5 mg/kg/day [33].

Amphotericin B
For patients with the most acutely life-threatening disseminated disease, and those few with meningitis, amphotericin B has been recommended. The recommended dose is 0.5–1 mg/kg/day [33, 34].

Fluconazole
Fluconazole is less effective than itraconazole and is given to patients who do not tolerate or have drug interactions with itraconazole. The recommended dose is 400 mg/day for 6 months [35, 36].

Terbinafine

Terbinafine has high activity against *S. schenckii* in vitro, but is reserved for cutaneous disease only at a daily dosage of 250–500 mg for 3 or 4 months [32].

Thermotherapy

Thermotherapy may be given as local heat or cryotherapy. Heat (42°C for 30 min twice a day) can also be used in combination with antimycotics or alone in cases where they are contraindicated, such as pregnancy or when poorly tolerated [32].

Chromoblastomycosis

Chromoblastomycosis (CBM) is a chronic fungal infection of the skin and subcutaneous tissue. The infection usually results from a traumatic injury and inoculation of microorganism from a specific group of dematiaceous fungi. In the tissues, fungi produce characteristic dark-colored, thick-walled, muriform cells, i.e., sclerotic cells (Medlar bodies).

Epidemiology

Originally described by Pedroso e Gomes in 1914 in the city of São Paulo (Brazil), CBM is distributed worldwide, being more prevalent in tropical and subtropical countries, mainly Brazil, Mexico, Cuba, and the Dominican Republic. In Brazil, Rio Grande do Sul, São Paulo, Rio de Janeiro, Minas Gerais, and states of the Amazonian region are endemic areas [37].

Fungi responsible for CBM are part of the microbiota, which decomposes organic matter in soil and water, and they also appear on the plants [38].

The disease is predominantly found in males from 30 to 50 years of age, especially rural workers, such as farmers and loggers. It mostly affects lower limbs, especially feet, which are most frequently exposed to contact with the infected material, e.g., soil, plants, or rotting wood [38].

Etiopathogenesis

The most frequently isolated organisms in CBM are *Fonsecaea pedrosoi*, *Phialophora verrucosa*, *Cladosporium carrioni*, and less frequently, *Rhinocladiella aquaspersa* [37].

The fungus penetrates the skin usually as a result of traumatic implantation. Especially in areas not protected by vestments, lesions develop on the site of the inoculation, locating themselves in the skin and, sometimes, in the subcutaneous tissue.

Clinical Presentation

A primary lesion is represented by an erythematous papule or a warty growth, which gradually enlarges from the site of infection, assuming various forms and sizes.

In advanced stages of the disease, dissemination may occur in the form of satellite lesions that arise from scratching autoinoculation and spread via the lymphatic system. Clinical changes progress slowly and frequently; the period from infection to diagnosis is 10 years [38].

CBM can present clinically in five different forms: nodular, tumoral, verrucous, plaque, and cicatricial (Fig. 11.16a, b). Severe secondary infection, lymphedema, elephantiasis and, more rarely, squamous cell carcinoma may occur secondarily [38].

Complementary Examinations

Potassium hydroxide-cleared specimen obtained from skin scrapings or histopathologically: presence of Medlar bodies (Fig. 11.17). Microbiological culture is essential to determine an etiologic agent. Culture is performed in Sabouraud agar and Sabouraud with antibiotics, where the fungi grow slowly and form black colonies [38, 39].

CBM is histopathologically characterized by pseudoepitheliomatous hyperplasia with histiocytes and neutrophils surrounding distinct copper-colored Medlar bodies (6–12 μm), which are fungal spores [40].
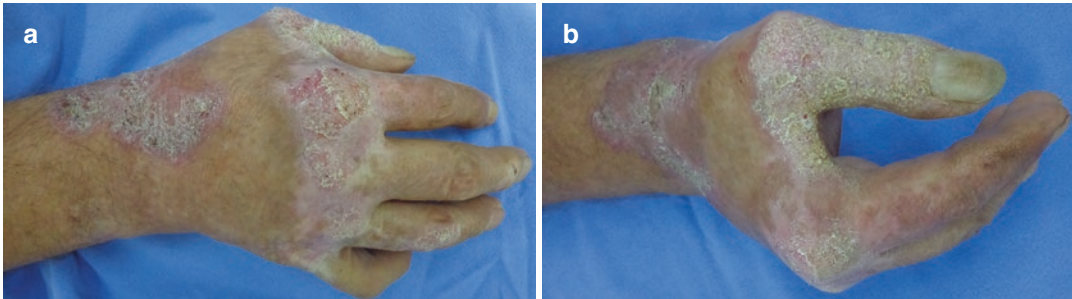
Fig. 11.16 (**a**, **b**) Chromoblastomycosis: verrucous plaque on the hand

Fig. 11.17 Chromoblasto-
mycosis: sclerotic bodies
(Courtesy of Prof. Sydney
Hartz, Alves)
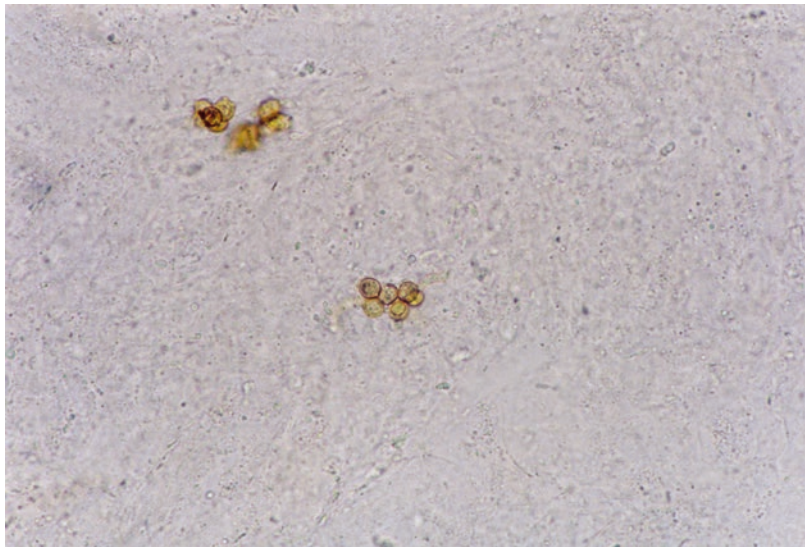
Differential Diagnosis

The most important differential diagnoses are
tuberculosis, sporotrichosis fixed form, leish-
maniasis, paracoccidioidomycosis, squamous
cell carcinoma, keratoacanthoma, sarcoidosis.
and lupus erythematosus.

Diagnosis

> **Box 11.10 Diagnosis of Chromoblastomycosis**
> Standard diagnosis is based on clinical pre-
> sentation and on the presence of Medlar
> bodies (skin scrapings or histopathologic
> sample). Culture determines the etiologic
> agent.

Therapeutic Approach

The therapeutic approach to CBM can be chal-
lenging, as no standard treatment has been estab-
lished and therapy can be complicated by low
cure rates and high relapse rates, especially in
chronic and extensive disease.

Treatment options can include thermotherapy,
cryotherapy, or surgical excision for small lesions
in combination with systemic antifungals.
Itraconazole (200–400 mg daily) for at least
6 months has been reported to have up to a 90%
cure rate with mild to moderate disease, but less
than 50% with severe disease. Combination oral
antifungal treatment with itraconazole and terbi-
nafine (250–1,000 g/day) has been recommended
[38, 40, 41]. Fluconazole 200–600 mg/day,
posaconazole 800 mg/day, and 5-flucytosine

50–150 mg/kg/day can also be prescribed. There are reports of progression of chromoblastomycosis to squamous cell carcinoma, which is rare and occurs after long-standing, inadequately treated lesions [38, 40, 41, 42].

Phaeohyphomycosis

The term phaeohyphomycosis (from the Greek *phaios*, meaning dark or darkish) was introduced by Ajello et al. in 1974 to designate infections by phaeoid or pigmented filamentous fungi that contain melanin in their walls [43–45].

The designation of tinea nigra, black piedra, and chromoblastomycosis (CBM) should not be replaced by phaeohyphomycosis. For example, in cases of chromoblastomycosis, muriform cells with septation along one or two planes in different levels are observed in the tissue (Medlar bodies), which do not fall into this classification [46].

Epidemiology

Subcutaneous manifestations of this mycosis are more frequent and develop among healthy individuals. On the other hand, systemic phaeohyphomycosis mainly occurs in immunocompromised patients. Phaeohyphomycosis may affect adult individuals of both genders and all races and is considered rare, especially in healthy individuals. In recent years the frequency of fungal infections has been increasing, as a consequence of interventions that affect the host's immune system [45].

The mycosis is more prevalent in humid tropical and subtropical climates, and the fungi are commonly found in soil [44].

Etiopathogenesis

It has been described 109 species and 60 genera. The most frequent etiologic agents described worldwide belong to *Alternaria* sp., *Exophiala* sp., and *Phialophora* sp. genera, among some 40 other organisms. *Phialophora verrucosa* has also been commonly described [44].

Virulence factors for the development of the disease include the production of melanin and carotenoids, which are deposited in the cell walls of melanized fungi and play an important role in pathogenicity [44, 46].

Clinical Presentation

Subcutaneous

The most common presentation is the mycotic cyst, which presents itself as a nodule or subcutaneous cyst, usually single and asymptomatic, after inoculation of the fungus by trauma on site. Most frequently, it affects the ends (Fig. 11.18a, b) [44].

Systemic

This is an uncommon presentation form and is more prevalent in immunocompromised patients, who may have very severe cases. It can reach
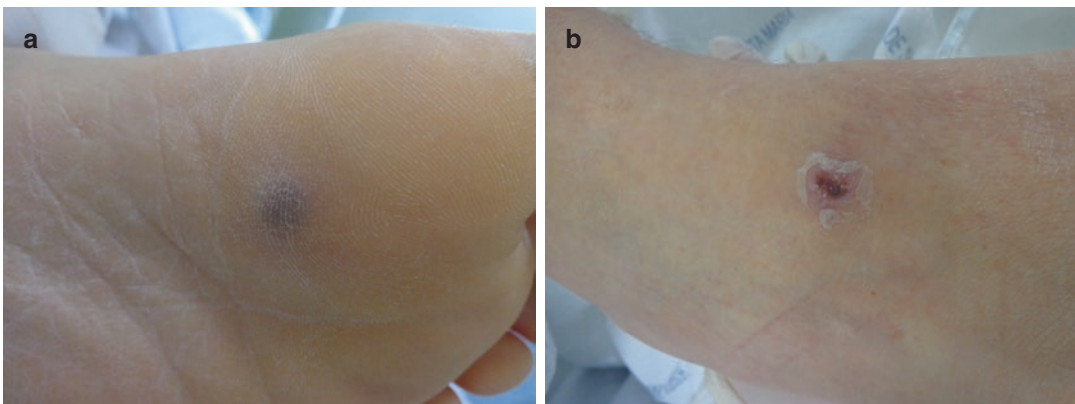
Fig. 11.18 (**a**) Purple painless nodule under the skin on the sole of the left foot, caused by *Alternaria* sp., in a neutropenic patient. (**b**) Ulcer on the anterior shin in the same patient (*Alternaria* sp.)

several organs, particularly the lungs and CNS. *Cladosporium bantianum* has been implicated most frequently [47].

Complementary Examinations

Pathologic examination of clinical specimens and careful gross and microscopic examination of cultures, which identifies the agent. Dematiaceous fungi can frequently be discerned in tissue specimens stained with conventional hematoxylin and eosin (HE); they appear as septate, brownish hyphae or yeast-like cells, reflecting their high melanin content. Masson–Fontana staining for melanin confirms their presence [44, 48].

Diagnosis

> **Box 11.11 Diagnosis of Phaeohyphomycosis**
> Clinical presentation, histopathologic examination, and microscopic examination of cultures, which identifies the agent.

Differential Diagnosis

Lipomas, fibromas, foreign body granuloma, epidermal cysts, and bacterial abscess.

Therapeutic Approach

Surgical excision is the standard treatment for localized lesions, which may be associated with an oral antifungal, such as itraconazole (200–400/day), for 6 months at least [44]. There are no standardized therapies for treatment of systemic phaeohyphomycosis. However, the triple combination of amphotericin B, 5-fluorocytosine, and itraconazole has been associated with improved survivalin this scenario. In addition, combination antifungal therapy (two or three drugs, at least one of which is an azole) is recommended for cerebral abscesses when surgery is not possible. In immunocompromised patients, clinical outcomes are generally poor regardless of treatment [46].

Hyalohyphomycosis

Unusual fungal agents that exist environmentally as saprophytes can often lead to opportunistic infections. Hyalohyphomycosis is a group of fungal infections caused by fungi characterized by colorless cell walls (hyaline septate hyphae) and can infect both immunocompetent as well as immunocompromised patients [49, 50].

Epidemiology

These fungi are ubiquitous in soil and decaying vegetable matter, and also can be found in polluted water [49–51]. They are capable of causing a wide variety of infections: disseminated infection occurs mainly in immunocompromised patients, the majority being stem cell and solid organ recipients. Diabetes and renal failure have also been described as risk factors [52].

Etiopathogenesis

The most frequent etiologic agents described worldwide belong to *Scedosporium* sp. (*Scedosporium apiospermum* and *Scedosporium prolificans*), *Fusarium* sp. (*Fusarium solani*, *Fusarium oxysporum*, and *Fusarium moniliforme*), *Paecilomyces* sp. (*Paecilomyces lilacinus* and *Paecilomyces variotii*), *Acremonium* sp., and *Trichoderma* sp., among some 40 other organisms [49–51].

Clinical Presentation

Localized

Cutaneous mycosis results from inoculation of the fungi into disrupted dermis and can occur in patients with little or no underlying immunodeficiency. The extremities and the corneas are often affected sites, and *Fusarium* is one of the more common causes of keratitis worldwide. These molds can also produce superficial cutaneous infections, such as onychomycosis, with or without paronychia, and toe-web intertrigo [50, 51].

Systemic

Systemic disease occurs mostly in immunocompromised patients and can cause invasive and disseminated infection with high mortality rates. It can affect many organs and systems, but the CNS and lungs are the most frequently involved sites [51]. Fusariosis has been described as a life-threatening and increasingly important mycosis in immunocompromised hosts, since
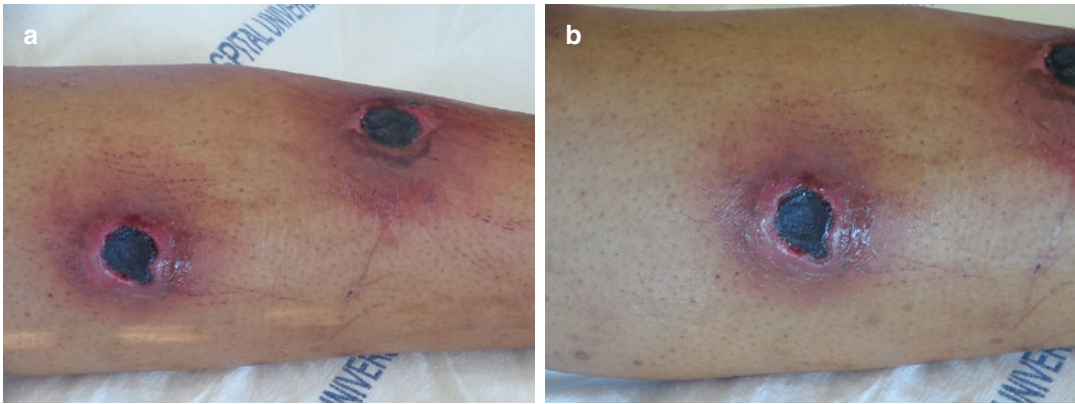
Fig. 11.19 (**a**, **b**) Ecthyma gangrenosum-like lesions caused by *Fusarium solani* in an immunocompromised patient
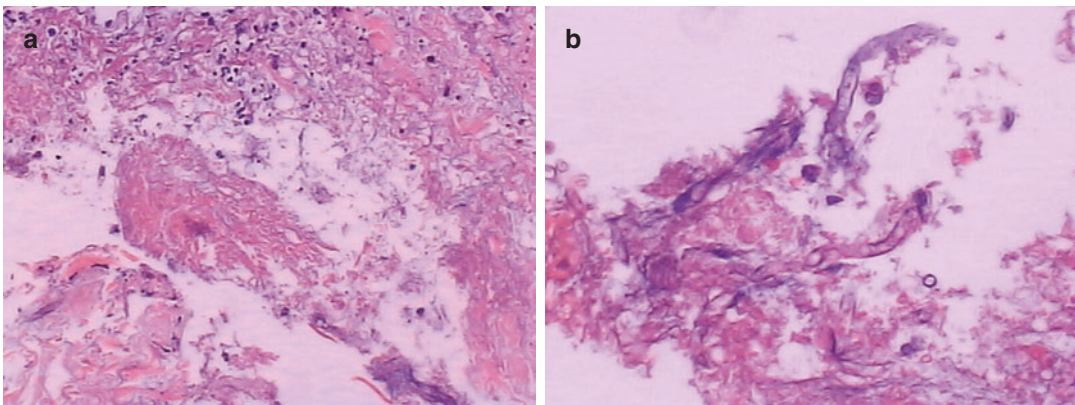
Fig. 11.20 (**a**, **b**) Biopsy specimen from ecthyma gangrenosum-like lesion caused by *Fusarium*: abscessed material and presence of nonpigmented, septate hyphae with acute-angle branching

these fungi are angiotropic and angioinvasive, leading to hemorrhagic infarction and low tissue perfusion, which results in tissue necrosis (Fig. 11.19a, b) [52]. Because the clinical presentation of fusariosis may be nonspecific, differentiating fusariosis from invasive aspergillosis can be challenging since these molds are clinically and histopathologically indistinguishable (Fig. 11.20a, b) [52, 53].

Complementary Examinations

In localized forms, diagnosis can be easily confirmed by direct microscopic examination. Otherwise, in systemic disease, confirmation of the diagnosis is obtained by culture to identify the fungus, owing to histopathologic similarities among the molds and the variable susceptibility of these fungi to antifungal agents [49, 51].

Diagnosis

> **Box 11.12 Diagnosis of Hyalohyphomycosis**
> Clinical presentation, direct microscopic examination, culture (more important for systemic disease).

Differential Diagnosis

Bacterial infection, atypical mycobacterial infections, aspergillosis and other fungal infections, amoebiasis, lipoma, panniculitis, lymphoma, pseudolymphoma, and sarcomas.

Therapeutic Approach

Hyalohyphomycosis treatment depends on the site of the infection. Surgical removal with or

without azole antifungal topical therapy is the choice for local disease. Systemic disease carries a poor prognosis despite aggressive antifungal therapy. Treatment options are limited by the lack of consistent and reliable activity of antifungal agents against these molds, and drugs such as the newer azole antifungals and amphotericin B lipid complex may be attempted. Results may vary, depending on the causal agent and its susceptibility to the drug [49, 51].

Lobomycosis (Jorge Lobo's Disease)

Lobomycosis is a chronic fungal infection also known as Jorge Lobo disease, Jorge Lobo mycosis, lacaziosis, keloidal blastomycosis, false leprosy, blastomycoid granulomatosis, and Amazon blastomycosis [54, 55].

Epidemiology

Lobomycosis is caused by the fungus *Lacazia loboi*, whose biogeographic complex is situated in rainforest areas. Most of the cases have been described in the tropical region of the Amazon region (Brazil and Colombia) where hot and humid climate favor the development of fungus. There are cases reported in other countries (e.g., Central America). Furthermore, imported cases have been reported in North America and Europe [54, 55].

This fungal infection is more common in males (male to female ratio 10:1), between 20 and 40 years old. Classically it affects people who live or work in forest or rural areas, such as gold and precious stone prospectors, rubber tappers, forest exploiters, and hunters. However, the ecologic niche of the fungus is expanding and cases have been described in dolphins [54, 55].

Etiopathogenesis

L. loboi is a saprophytic fungus in soil, vegetation, and water. Transmission occurs by inoculation from a bite or sting from an arthropod, snake, or stingray, or trauma from a cutting instrument. There are no reports of person-to-person transmission [56]. Once on the dermis, the pathogen stimulates the development of a granulomatous reaction, and after the proliferative phase there is a possibility of a dissemination phase through lymphatics [55].

Clinical Presentation

Lobomycosis is classified as localized or isolated disease, multifocal disease (restricted to an anatomic area), or disseminated disease (more than one anatomic segment). Lesions can be infiltrative, gummatous, ulcerative, verrucous, tumoral, sclerodermiform, macular, plaques, or nodular, the most common presentation. Often the lesion resembles a scar or a keloid. The surface color varies from normochromic to erythematous-brownish or red-wine, with or without telangiectasia. It is preferably located in the lower limbs, ears, and upper limbs. Lesions are generally asymptomatic, but pruritus and dysesthesia can occur [54, 55].

Complementary Examinations

L. loboi is found in great amounts upon direct examination and histologic preparations. Direct examination reveals an abundance of fungi with thick refringent and double-contour walls. Histopathologic examination is pathognomonic and reveals granuloma with a dense histiocytic infiltrate composed of multiple epithelioid and multinucleated giant cells. The parasites are inside the histiocytes in the dermis and among the scales and scaly crusts of the stratum corneum, observed as black spots on the skin that covers the ulcerated crusted lesions. Fungi can be better visualized with silver stains [54–56].

Diagnosis

> **Box 11.13 Diagnosis of Lobomycosis**
> Clinical aspects of lesions, epidemiologic date, provenance of endemic areas, direct mycologic and histopathologic examination.

Differential Diagnosis

The differential diagnosis must include keloid, leprosy, mucocutaneous leishmaniasis, other deep mycoses, lymphomas, and cutaneous metastases, among others [54].

Therapeutic Approach

Surgical excision, electrocauterization, and cryo-surgery are treatment options, particularly for minor lesions. At present there is no optimal drug treatment. Clofazimine 100–300 mg daily is indicated, although the treatment time is not well established. Itraconazole has been shown to be partially effective as an adjuvant to prevent recurrence of surgically removed lesions, while posaconazole has been reported to be effective in reducing the lesions after 75 weeks of treatment [55, 56].

Mycetoma

Mycetoma is an uncommon chronic infective disease of the skin and subcutaneous tissues characterized by the triad of tumefaction, draining sinuses, and presence of colonial grains in the exudates. Infection can be caused by true fungi in 40% of cases when it is known as eumycetoma, and by filamentous bacteria of the order Actinomycetes (actinomycetoma) in 60% of cases [57].

Epidemiology

Minor trauma allows the causative organism from the soil to enter the skin (e.g., cut on the hand, foot splinter, local trauma related to carrying soil-contaminated material). A neutrophilic response initially occurs, which may be followed by a granulomatous reaction. Spread occurs through skin facial planes and can involve the bone [57, 58].

Mycetoma typically presents in young men and rural workers or in individuals who walk barefoot in dry, dusty conditions. The most common site of occurrence is the foot (approximately 70% of cases) or lower leg, with infection of the dorsal aspect of the forefoot being typical. The hand is the next most common location; however, mycetoma lesions can occur anywhere on the body [57, 59].

It is endemic in the tropics and subtropics, and is named after the region of India (Madura: "Madura foot") where it was first described in 1842 [57, 59].

Etiopathogenesis

More than 30 species have been identified to cause mycetoma. Actinomycetoma is caused by a group of filamentous bacteria, among which *Nippostrongylus brasiliensis* and *Streptomyces madurae* are the most common. Eumycetoma is often due to *Allescheria boydii*, *Madurella griesia*, and *Madurella mycetomatis*: the most isolated agent worldwide [60].

Clinical Presentation

The clinical presentation of eumycetoma and actinomycetoma is similar.

The earliest sign of mycetoma is a painless subcutaneous swelling. Following the initial injury the disease typically follows a slow chronic course over many years with painless swelling and intermittent discharge of pus. After some years massive swelling of the area occurs, with induration, skin rupture, and sinus tract formation. As the infection spreads, old sinuses close and new ones open [58, 61].

The exudates are typically granular and pain may occur because of secondary bacterial infection or bone invasion.

Complementary Examinations
Direct Examination

Direct examination is essential for diagnosis, which reveals the presence of grains in the secretion obtained from injury. The size, shape, and color of the grains are important in the identification of the causative agent: tissue Gram stain to detect fine, Gram-positive, branching filaments within the actinomycetoma grain and Gomori methenamine silver or periodic acid-Schiff (PAS) stain to demonstrate the larger hyphae of eumycetoma. The presence of a black grain directs the diagnostic of eumycetoma, since actinomycetoma grains do not produce this color [58, 62].

Culture

The cultures can be performed using SDA, brain heart infusion (BHI) agar, and blood agar. Superficial samples of the draining sinuses are inadequate for culture because of frequent contamination with bacteria. Sample to culture should be obtained from a deep-wedge biopsy or via puncture and fine-needle aspiration [62].

Histopathology

Biopsy material stained with HE shows grains or colonies within abscess cavities with or without surrounding granulomatous reaction. There is no difference between the granulomas of actinomycetomas and eumycetomas. However, if the colonies are Gram-positive and show filamentous bacteria less than 1 μm thick, actinomycetes should be considered. If the colonies show PAS-positive hyphae 2–6 μm thick, eumycetes should be considered [57].

Image

Plain X-rays are used to assess for evidence of bone involvement. Computed tomography scanning may be more sensitive in the early stages. Magnetic resonance imaging scans can provide a better assessment of the degree of bone and soft tissue involvement, and may be useful in evaluating the differential diagnosis of the swelling [57, 58].

Diagnosis

> **Box 11.14 Diagnosis of Mycetoma**
> Clinical presentation, microscopy and culture of exudates, histopathologic examination, and culture from sample of skin biopsy.

Differential Diagnosis

Differential diagnosis includes chronic bacterial osteomyelitis, cutaneous tuberculosis, chromomycosis, botryomycosis, coccidioidomycosis, leishmaniasis, sarcomas, and other malignancies of bone and soft tissue [57, 58].

Therapeutic Approach

Because of the slow, relatively pain-free progression of the disease, mycetoma is often at an advanced stage when diagnosed. In addition, medical treatment of mycetoma depends on its fungal or bacterial etiology. Bone involvement complicates clinical management, often leaving surgical amputation as the only treatment option.

Eumycetoma

The combination of medical and surgical treatment is the usual management of this fungal infection.

Treatment is based on prolonged administration of imidazoles such as itraconazole, alone or combined with terbinafine. Posaconazole and voriconazole are available but are expensive; amphotericin B is rarely used [63].

Actinomycetoma

Actinomycetoma must be treated with trimethoprim-sulfamethoxazole alone or in combination with other available antibiotics. Amikacin has been proved effective in disseminated infections or cases resistant to previous therapy. Carbapenems are useful in some disseminated infections [63].

Mucormycosis and Entomophthoromycosis (or Entomophthoramycosis)

Epidemiology

Zygomycota is an artificial grouping that contains a heterogeneous group of fungi; for this reason, the name zygomycosis is out of date. The disease is very rare; however, it is importantly severe, with a mortality rate higher than 50%. Immunocompromised hosts, transplant recipients, and diabetic patients are more predisposed to this infection. Malnutrition, cytomegalovirus infection, trauma, and extended wounds/burns are also predisposing conditions. Patients with AIDS are not more predisposed than other people, because T lymphocytes are not key players in fighting against Zygomycota infection [64].

Orders Mucorales and Entomophthorales contain most of the human pathogenic Zygomycota. The true prevalence among the general population is not known, since published data are conflicting. In patients with hematologic diseases, Mucorales are one of the most common agents of systemic mycoses, as well as *Aspergillus*, *Candida*, and *Fusarium*. Since the higher incidence of hematologic malignancies in men, these fungi are also more prevalent among males [64].

Mucorales are ubiquitous in the environment and present worldwide in the soil, infecting plants and other fungi. Entomophthorales are fungi of tropical or subtropical distribution that represent more than 250 entomopathogenic, soil, and litter-associated species. While mucormycosis is a very aggressive invasive fungal infection, entomophthoromycosis is usually localized [64, 65].

Etiopathogenesis

The main route of infection for Mucorales and Entomophthorales is the respiratory system, from the inhalation of spores; direct inoculation and ingestion of fungal propagules have also been described. Innate immunity is imperative to fight this fungal infection, while the involvement of acquired immunity is not so pronounced [64].

Mucormycosis

Mucorales have great capacity for hematogenous dissemination, enabling rapid spread to organs and adjacent structures. This fact has contributed to the high mortality rate of this disease. *Rhizopus oryzae* and *Rhizopus rhizopodiformis* are the most prevalent species in human infections. Other genera implicated are *Lichtheimia*, *Mucor*, *Rhizomucor*, *Cunninghamella*, and *Apophysomyces* [65].

Entomophthoromycosis (or Entomophthoramycosis)

Entomophthorales produce chronic, usually subcutaneous infections without invasion of blood vessels [65]. *Basidiobolus* and *Conidiobolus* are the genera that cause human infection. These fungi have a predilection for areas with adipose tissue, which would justify the development of more restrictive disease than Mucorales. Immunocompetent individuals are more commonly affected, but the infection is not restricted to them [66].

Clinical Presentation

Mucormycosis

The clinical presentation of mucormycosis includes five forms: rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated. Rhinocerebral mucormycosis is the most common clinical presentation in both neutropenic hematologic and diabetic patients. It manifests by necrotic black lesions on the hard palate, necrotic turbinates, and septum perforation. Patients report headaches, altered mental status, fever, and ocular symptoms as lacrimation, irritation, and periorbital anesthesia. The symptoms of pulmonary and gastrointestinal mucormycosis are nonspecific. In immunocompetent and otherwise healthy patients, the most prevalent presentation is the cutaneous/subcutaneous form. Ulcer, cellulite, ecthyma gangrenosum-like lesion, and necrotic abscess may occur. Disseminated mucormycosis is characterized by the involvement of two or more noncontiguous organs [64, 67].

Entomophthoromycosis

There are two clinically distinct forms: basidiobolomycosis and conidiobolomycosis. Basidiobolomycosis manifests as an erythematous and warm, disc-shaped, rubbery, mobile masses that may be quite large. This subcutaneous form presents as painless firm erythematous plaques, with eventually significant non-pitting edema. It can evolve with skin ulceration and lymph node enlargement. The most common sites are shoulder, hips, and thighs. The evolution is slowly progressive and the systemic dissemination is extremely uncommon [66].

Conidiobolomycosis is usually restricted to the rhinofacial area and presents as a firm swelling of the upper lip or face. It can spread by contiguity through the nasal bridge and the upper and lower face, including the orbit. Intracranial extension is uncommon. The symptoms implicated are nasal drainage and obstruction. There may be paranasal sinus pain [66].

Complementary Examinations

Although direct examination has been limited, it is useful for the diagnostic suspicion. Cultures are often negative even though direct microscopy is positive. When culture is positive, it can help in the species identification and antifungal drug susceptibility testing.

Histopathologic analysis reveals broad, non-septate hyphae, which branch at a right angle. The presence of tissue infarction, necrosis, and thrombosis are characteristic [64, 66, 68].

Diagnosis

Box 11.15 Diagnosis of Mucormycosis and Entomophthoromycosis
Clinical suspicion, imaging studies, culture, and histopathology. The direct identification of the characteristic hyphae or retrieval of the organism in culture allows conclusive diagnosis. Tissue specimens, sputum, paranasal sinus secretions, and bronchoalveolar lavage fluid are appropriate samples for this analysis.

Differential Diagnosis

Mucormycosis
The clinical picture can be similar to other deep mycoses caused by *Aspergillus*, *Scedosporium*, and *Fusarium* [64].

Basidiobolomycosis
The main differential diagnoses are tuberculosis, localized elephantiasis, onchocerciasis, scleroderma, Burkitt's lymphoma, and Wegener granulomatosis [66].

Conidiobolomycosis
The differential diagnoses include cellulitis, rhinoscleroma, lymphoma, and sarcoma [66].

Therapeutic Approach
Early diagnosis and treatment are critical to avoid an unfavorable outcome. The combined treatment, including antifungal therapy and surgical debridement, is the outstanding option. The resistance to the routinely used antifungals, such as azoles (except posaconazole) and echinocandins, is high, which hampers proper treatment. Amphotericin B is the gold standard of therapy. Liposomal amphotericin B is most suitable because of fewer side effects. Optimal dosage is not known, ranging between 5 and 10 mg/kg intravenously per day. Posaconazole must be regarded as a second therapeutic choice, alone or in combination with amphotericin B, especially in severe cases of invasive mucormycosis. The recommended dose of posaconazole is 200 mg orally four times per day. The combination of liposomal amphotericin B and echinocandin is the most promising combined therapy because of bioavailability of parenteral formulations and synergy. The optimal duration of the therapy has not been established, and continuation of the treatment until resolution has been proposed [64, 65, 67].

Paracoccidiodomycosis

Paracoccidioidomycosis (PCM) is a human systemic mycosis whose etiologic agent is *Paracoccidioides brasiliensis*, a thermodimorphic fungus that promotes a chronic inflammatory granulomatous disease [69].

Epidemiology
This is the most important systemic mycosis in Latin America with Brazil, Venezuela, and Argentina being the countries with the greatest number of patients. The occurrence in Brazil, which accounts for 80% of the cases, is concentrated in its southeastern, southern, and midwestern regions. PCM is an endemic mycosis that is responsible by the highest cause of mortality and the eighth most important cause of mortality from chronic infectious diseases. An estimated 3,360 new cases per year reflect the fatality and mortality rates attributed to PCM in Brazil. Nonautochthonous cases have been described outside endemic areas in patients who have lived in or visited Latin America. The disease is not restricted to humans, also being described in different species of domestic and wild animals [70, 71].

PCM infection does not favor gender or ethnicity, whereas PCM disease affects mainly adult male rural workers in constant contact with vegetation and soil during the most productive period of their lives, which implies important economic

repercussions for patients and their dependents. Poor hygiene, malnutrition, smoking, and alcohol consumption are considered risk factors for the manifestation of the disease [69, 72].

The clinical forms of PCM were classified based on the relationship between clinical aspects and the natural history of the disease. Thus, the infection is related to the patient without signs and symptoms of the disease but with a positive paracoccidioidin skin test reaction. Patients with PCM disease are divided into two groups: the subacute variety, which accounts for 5% of cases, affects mostly young adults, and is associated with a high mortality rate; and the chronic progressive adult form, which accounts for the majority of cases and affects predominantly males between the ages of 30 and 60 years [71, 72].

Paracoccidioidomycosis is an AIDS-associated opportunistic infection. However, the incidence is lower than that expected by comparison with other endemic fungal infections [70, 71].

Etiopathogenesis

P. brasiliensis is a dimorphic fungus implicated as a cause of this disease. *Paracoccidioides lutzii*, whose endemic area involves the midwestern and northern regions of Brazil, is another species recently identified within the genus *Paracoccidioides*. However, the characteristics of the disease caused by *P. lutzii* are still poorly known [70, 71].

P. brasiliensis infection occurs through the respiratory tract: when infectious propagules (hyphal fragments or conidia) are inhaled, they are deposited in the human lungs and the morphology of the fungus differentiates to yeast form by increasing the temperature to 36°–37°C, thus establishing the disease. Infection by traumatic injury is unlikely. There is no evidence of human transmission of paracoccidioidomycosis [70, 73].

P. brasiliensis express cell surface proteins called adhesins, which are responsible for the first contact with the host cells and contribute to host colonization and cell invasion. The immune response against *P. brasiliensis* infection will define the disease. When Th1 cytokine profiles prevail, notably interleukin (IL)-12, interferon-γ, and tumor necrosis factor α, a subclinical infection will develop. On the other hand, expression of a dominant T-helper 2 immunity consisting of production of specific immunoglobulin (Ig)E and IgG antibody subclasses and high levels of IL-4, IL-5, and IL-10, the evolution will transition to clinical disease. In acute/subacute form, the disease develops a few weeks or months after infection with *P. brasiliensis*. The chronic form of the disease manifests only months to years after *P. brasiliensis* infection [70, 72].

Clinical Presentation

The *P. brasiliensis* infection may be classified as shown in Table 11.4 [71].

The less common form of PCM is the subacute variety (juvenile type), which affects mostly young adults, has a rapidly progressive course, and is associated with a high mortality rate. It is characterized by involvement of the phagocytic-mononuclear system, and symptoms include fever and weight loss and mild/moderate anemia for 2–3 months or longer. Cervical, axillary, and inguinal nodes are the most commonly enlarged. Lymph nodes are initially hard but evolve with inflammatory signs and sometimes become fluctuant. The liver and spleen are often moderately enlarged and bone marrow may be involved. Multiple skin and mucosal lesions may occur. In approximately 50% of cases, the digestive tract is also affected [71, 74, 75].

Table 11.4 Classification of *P. brasiliensis* infection

Clinical manifestation	Description
Paracoccidioidomycosis infection	Subclinical, detected only by skin-test positivity
Paracoccidioidomycosis disease	Acute or subacute form: there is a tropism of the fungus to the reticuloendothelial system
	Chronic form: usually unifocal when a single organ is affected, such as lungs, or multifocal, affecting more than one organ, mainly the lungs and the oral mucosa
Sequelae of paracoccidioidomycosis	Features as chronic obstructive pulmonary disease, dysphonia, and laryngeal scarring may be present

The chronic form of the disease accounts for more than 90% of cases and characteristically presents an insidious and chronic evolution, usually with mild or moderate severity but resulting in sequelae in about one-third of cases. The lungs are the most commonly affected organ (80%), followed by the skin and mucous membranes (oral, larynx, trachea, and digestive tract). Adenopathy, occasionally complicated by draining sinuses, may involve cervical, axillary, or mediastinal lymph nodes. Adrenal involvement can range from subtle adrenal dysfunction to overt insufficiency. Involvement of the vascular system, CNS, spleen, liver, and male genitourinary tract have been reported less commonly. Patients may complain of weakness, weight loss, dyspnea, cough, sometimes purulent sputum, and, rarely, hemoptysis. Fever is uncommon and, when present, secondary pulmonary infection or association with TB should be suspected. As the course is chronic, when patients present with dyspnea a marked contrast is observed between the paucity of clinical symptoms and signs and the multiple findings on chest radiography. The oral, pharyngeal, and laryngeal mucosal tissues are involved in up to 70% of adult patients. The classic clinical presentation is a superficial ulcer with granular appearance and hemorrhagic points (mulberry-like stomatitis/infiltrative moriform stomatitis). Hoarseness and dysphonia occur in association with laryngeal lesions and may evolve with laryngeal obstruction. PCM frequently attacks the skin. Cutaneous lesions may originate from contiguous lesions (neighboring mucosae, fistula formation from lymph nodes, or from a focus of osteomyelitis), from hematogenous dissemination, or, rarely, from direct inoculation of *P. brasiliensis* into the skin. Lesions can be extremely polymorphic but often appear as warty, hyperkeratotic plaques or ulcerative, crusted lesions, mainly on the face around the mouth and nose (Fig. 11.21). Lesions caused by hematogenous dissemination tend to be multiple, initially papuloacneiform, and later ulcerative or even verrucous [71, 74, 75].
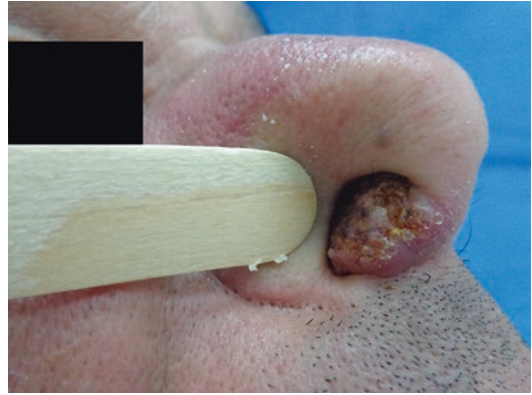
Fig. 11.21 Paracoccidiodomycosis: ulcerative, crusted lesion on the face around the nose

Patients with AIDS acquire a form of PCM that resembles the subacute juvenile type with tropism to the phagocytic-mononuclear system, and probably results from reactivation of a latent focus [70, 75].

Complementary Examinations

The gold standard for diagnosis is based on correct identification of *P. brasiliensis* in clinical specimens or in tissue. Direct examination, using 10% potassium hydroxide applied to a smear sample, is effective and inexpensive (Fig. 11.22) [71, 76].

Histologic examination using silver methenamine or PAS stain tests is inexpensive and allows identification of the fungus. Spores are roundish and 6–20 mm in diameter. Budding is not common, but when seen is usually multiple and evidenced around the whole spore, so the whole budding structure can be up to 60 mm in diameter (Fig. 11.23). In the chronic form, the inflammatory infiltrate is composed mainly of epithelioid granulomas. Culture in Sabouraud agar should always be ordered but has low sensitivity [71, 72, 76].

Serology in PCM, besides helping to make the diagnosis, has application during and after the treatment, and in the follow-up. Currently double immunodiffusion, counter-immunoelectrophoresis,

Fig. 11.22 Potassium hydroxide (KOH) preparation; note the variation in cell size with Paracoccidioides
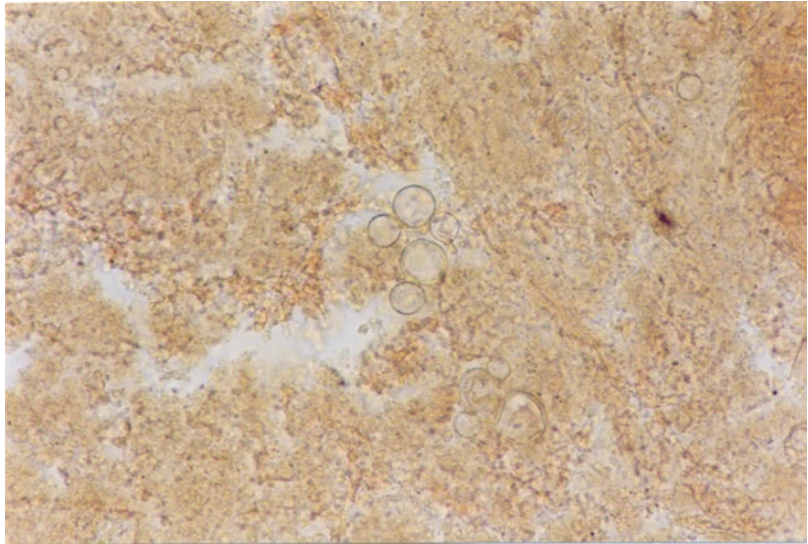
Fig. 11.23 *P. brasiliensis* budding yeasts are observed free on the stroma (Courtesy of Pathology Department, UFSM)
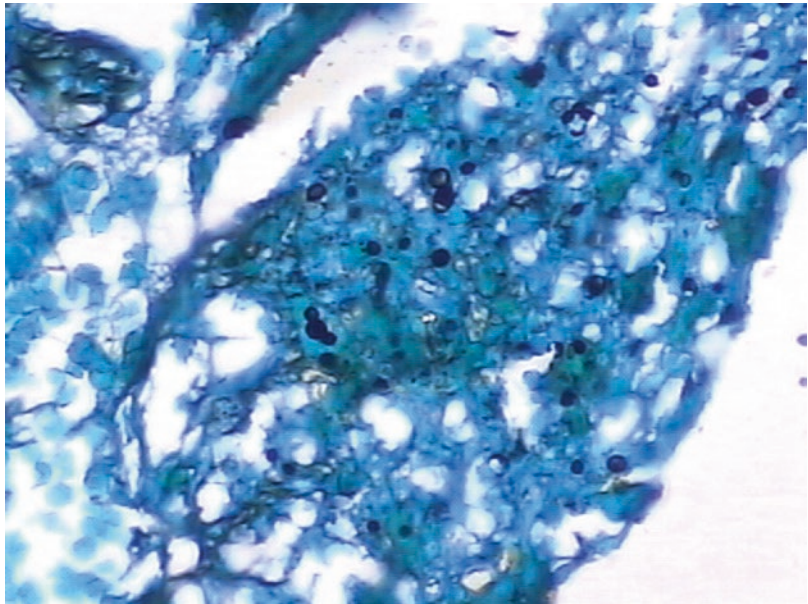
enzyme-linked immunosorbent assay (ELISA), and immunoblotting methods are available. The antigenic substrate is a fundamental part of these techniques, and *P. brasiliensis* has a complex antigenic structure. Thus, the fungus cell wall glycoprotein of 43 kDa, gp43, considered specific to *P. brasiliensis*, is the most important antigen for recognition of this fungus, representing the main antigen for the PCM diagnosis [69, 72, 74, 75].

X-ray imaging or computed tomography studies may be useful in diagnostic suspicion and show bilateral infiltrate, which is interstitial, micronodular, reticulonodular, or nodular, generally in perihilar or basal areas of the lungs [75].

Diagnosis

> **Box 11.16 Diagnosis of Paracoccidioidomycosis**
> Clinical presentation, and identification of *P. brasiliensis* in clinical specimens or in tissue.

Differential Diagnosis

The differential diagnosis must be made with tuberculosis, leishmaniasis, Hodgkin's disease, sarcoidosis, several systemic and subcutaneous mycoses, lung cancer, and squamous cell carcinoma, when the skin presentation is an isolated verrucous or ulcerative-necrotic lesion [71].

Therapeutic Approach

Treatment must be based on the severity in every individual and the affected organs. Itraconazole is considered the best option for mild to moderate clinical forms. The recommended dose is 200 mg daily for 6–9 months for mild disease and 200 mg daily for 12–18 months for moderate disease. Sulfamethoxazole-trimethoprim 2,400 mg plus 480 mg orally, daily for 12 months for mild cases is also a useful option. Moderate clinical forms are treated for 18–24 months at least. Voriconazole, a new second-generation triazoic antifungal, constitutes an important therapeutic alternative; however, its high cost is an important limitation [71].

Amphotericin B has been recommended since 1958 for the treatment of the most severe PCM cases, in conventional or lipid formulations. The dose varies from 0.5 to 1 mg/kg intravenously, daily until a total dose of 30 mg/kg is reached [71].

CNS disease treatment should include drugs that reach higher concentrations in cerebrospinal fluid and parenchyma. Fluconazole 400 mg daily for 3–6 months, with a maintenance dose of 100–200 mg daily for 6–12 months, has been successfully used as it presents good CNS penetration [71].

Coccidioidomycosis

Valley fever, also called coccidioidomycosis, is an infection caused by the fungus *Coccidioides*, which is known to live in the soil in the southwestern United States and parts of Mexico and Central and South America. Features such as high temperatures, low rainfall, and alkaline soil contribute to the development of the fungus [77].

Epidemiology

The incidence of *Coccidioides* spp. infection has increased in recent years, reaching annual rates close to 60 per 100,000 population in some regions. The most important risk factor is dust exposure in endemic areas, usually because of occupational and recreational activities. People at greatest risk include farmers, construction workers, and archaeologists. Travelers are at increased risk if they participate in activities that expose them to dust. Most cases follow a benign course, since only around 5% of cases become symptomatic and chronic. Pregnant women and immunosuppressed patients are considered risk groups for severe or disseminated disease [77, 78].

Etiopathogenesis

Coccidioides immitis and *Coccidioides posadasii* are the species highlighted as causes of coccidioidomycosis. They are dimorphic fungi and belong to the phylum Ascomycota. Although there are genetic differences between these species, they are clinically and microbiologically indistinguishable. Transmission of the disease occurs through inhalation arthroconidia, so the lung is the most commonly affected organ [77, 78].

Clinical Presentation

Coccidioidomycosis can be classified into two clinical spectra. Primary disease affects initially the lungs and patients develops a flu-like syndrome (fever, headache, profound fatigue, cough, pleuritic pain, and arthralgia), commonly known as "San Joaquin valley fever." Secondary disease is characterized by a chronic process or disseminated disease and involves other organs, including bones, joints, nervous system, and meninges [77].

Skin involvement includes a wide variety of clinical presentations. Cutaneous lesions include reactive manifestations of lung infection, such as erythema nodosum, erythema multiforme, acute

generalized exanthema, and Sweet's syndrome. Primary cutaneous infection by direct inoculation of the fungus is extremely rare and typically manifests as a painless, indurated nodule with ulceration (chancroid lesion). Secondary nodules may arise in a linear lymphatic sporotrichoid distribution [77].

Polymorphic and nonspecific skin lesions, such as papules, nodules, gummas, acneiform lesions, ulcerated and verrucous plaques, scars, abscesses, and fistulas reflect disseminated disease. In this case the face, neck, scalp, and chest wall are the most common sites, especially the nasolabial region [77].

Complementary Examinations

Direct mycology examination revels double-walled refractile spherules and endosporulation as characteristic. In culture at room temperature it grows as a white, cottony mold, with septate hyphae and barrel-shaped arthroconidia. Histopathology findings usually show suppurative granulomas that contain double-walled refractile spherules (10–80 μm) with endospores [77].

Serologic tests identifying anticoccidioidal antibodies represent optimal assays for the diagnosis and prognosis of coccidioidomycosis [77, 79].

Diagnosis

> **Box 11.17 Diagnosis of Coccidioidomycosis**
> Clinical presentation, culture, microscopy, and serology. Other diagnostic tools such as cutaneous tests, molecular diagnosis, and imaging studies are also used.

Differential Diagnosis

Important differential diagnoses include histoplasmosis, blastomycosis, cryptococcosis, tuberculosis, sarcoidosis, and primary skin malignancies [77].

Therapeutic Approach

Coccidioides infection is often self-limited and spontaneous resolution is common. When treatment with antifungal is indicated, treatment options are as follows [77, 79].

- Primary cutaneous coccidioidomycosis: itraconazole at doses of 400 mg per day for 6 months
- Primary pulmonary coccidioidomycosis without risk factors for dissemination, or less severe: fluconazole or itraconazole 400 mg per day for 3–6 months
- Primary coccidioidomycosis with risk factors: fluconazole or itraconazole 400 mg per day for 4–12 months
- Chronic pulmonary coccidioidomycosis: fluconazole or itraconazole 400 mg per day for 12–18 months
- Meningeal infection: fluconazole 400 mg per day (with initial doses of up to 1,000 mg per day) or itraconazole 400–600 mg per day for lifelong treatment
- For pregnant women and severe or refractory infections, the treatment of choice is intravenous deoxycholate amphotericin B at 0.7 mg/kg daily or a lipid preparation at 3 mg/kg daily

Histoplasmosis

Histoplasmosis, an infection caused by the dimorphic fungus *Histoplasma capsulatum*, is considered one of the most common fungal respiratory infections worldwide.

Epidemiology

The fungus is distributed worldwide but is endemic in certain areas of North and South America. In the United States, histoplasmosis is known to affect up to 90% of the residents of the Mississippi and Ohio River valleys [80].

H. capsulatum feeds on nitrogen-rich soils, especially those replete with bird and bat droppings. When inhabited soils such as these are disturbed, spores can become airborne and inhaled. Severity of illness after inhalation exposure to *H. capsulatum* varies depending on the intensity of exposure and the immunity of the host. Disseminated disease predominates in the immunocompromised individuals, particularly during infancy, HIV infection, hematologic malignancy, solid organ transplantation, and treatment with corticosteroids [80–82].
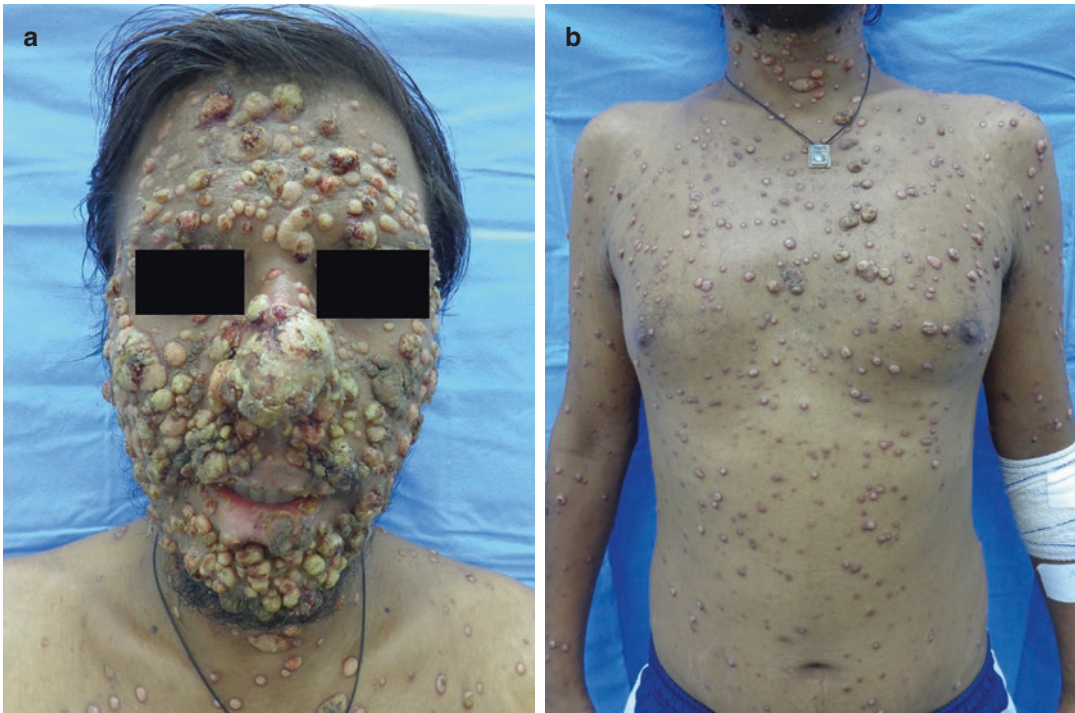
Fig. 11.24 (**a**) Histoplasmosis: disseminated papules with crusts on the face in an HIV-positive patient. (**b**) Disseminated giant molluscum-like lesions in the same patient

Etiopathogenesis

Humans are infected via inhalation of airborne microconidia, which the wind can carry for miles. Once in the lung the microconidia are converted into pathogenic yeast forms that disseminate hematogenously to multiple organs, including the spleen, liver, bone marrow, and lymph nodes [80, 81].

Clinical Presentation

The predominant clinical manifestation of histoplasmosis is pneumonia, but most patients have either no symptoms or mild pulmonary complaints. Hematogenous dissemination is common in the early stages of infection, but almost all people in whom this occurs remain asymptomatic. Symptomatic acute disseminated infection occurs almost entirely in those who are immunosuppressed. On the other hand, chronic progressive disseminated histoplasmosis occurs mostly in elderly individuals who have no known immunosuppression but who are unable to contain the organism.

Mucous membrane ulcers and skin lesions appear as subacute or chronic disseminated histoplasmosis [81, 82]. Skin lesions are polymorphic and nonspecific, such as papules, plaques with or without crusts, nodules, erosions or ulcers, pyoderma gangrenosum-like, molluscum-like lesions, or acneiform eruptions (Fig. 11.24a, b). The most commonly affected sites are the face, extremities, and trunk [82, 83].

Complementary Examinations

Direct microscopic examination using silver methenamine stain or Giemsa generally reveal intracellular yeast. Histopathologic examination with special staining (PAS and Gomori Grocott) allow the differential diagnoses, such as *Leishmania* and *Trypanosoma*. *H. capsulatum* is found in the yeast form inside or outside of macrophages, as budding, encapsulated yeasts [81–83].

Microscopy of culture shows microconidia and typical macroconidia, with tuberculated projections (echinulations) [81, 83].

Diagnosis

Box 11.18 Diagnosis of Histoplasmosis
Clinical presentation and all tissue or body fluid serve to direct microscopic examination, which is a simple and rapid diagnostic method. However, the gold-standard diagnosis is culture. Serology and antigen testing also may be useful [81, 82].

Differential Diagnosis

Especially in disease-endemic areas, tuberculosis is the main differential diagnosis of histoplasmosis, since symptoms of both are nonspecific. Skin lesions need differential diagnosis with molluscum contagiosum, pyoderma gangrenosum, and other deep mycoses [81, 83].

Therapeutic Approach

Early treatment allows better prognosis, since the mortality of disseminated disease is high. In view of the risk of relapse and severity of disseminated disease, a lifelong maintenance phase is indicated after the induction phase. For patients who are mildly or moderately ill, oral itraconazole, 200 mg three times daily for 3 days thence reducing dose to 200 mg, once or twice daily, is recommended. Fluconazole (800 mg daily) is indicated in patients who cannot take itraconazole. Amphotericin B is the therapeutic agent of choice for induction therapy in moderate to severely disseminated histoplasmosis. Conventional amphotericin B intravenously at 0.7–1 mg/kg daily should be used in initial phase for 12 weeks. The liposomal amphotericin B dose is 3–5 mg/kg daily. Itraconazole (200 mg, once or twice daily) is indicated in maintenance therapy [82].

Cryptococcosis

Cryptococcosis is a globally distributed invasive fungal infection caused by species within the genus *Cryptococcus*, which presents substantial therapeutic challenges.

Epidemiology

Cryptococcosis is the third most prevalent disease in solid organ transplant (SOT) recipients and HIV-positive individuals. HIV-positive individuals with a CD4 lymphocyte count of <100 cells/mm^3 are at highest risk for developing this disease, especially cryptococcal meningitis. End-stage liver disease, renal insufficiency, and sarcoidosis are also risk factors for this systemic mycosis. However, it can also affect patients without any recognized immunologic defect. Skin involvement is seen in 10–20% of systemic cryptococcosis [83–85].

The etiologic agents are the species *Cryptococcus neoformans* and *Cryptococcus gattii* (formerly designated as *C. neoformans* var. *gattii*). These bacilli can inhabit diverse environmental niches and substrates. *C. neoformans* is more commonly found in soil contaminated by the feces of birds in temperate climates and cold, urban areas. The main niche of *C. gattii* is the hollows of eucalyptus trees. This explains why *C. gattii* is more frequent in rural areas of tropical and subtropical regions as Brazil, Africa, Australia, and Southern California, although this yeast may adapt to a temperate climate [84, 85].

Etiopathogenesis

Cryptococcus are basidiomycetes and are encapsulated yeasts. Based on the capsule structure, they are grouped into the two varieties, *neoformans* and *gatti*, which include five serotypes [85].

These yeasts have a polysaccharide capsule, which increases their invasiveness and pathogenicity, and confers resistance to the environment and the host. Primary pulmonary infection occurs as a result of inhalation of fungus and may progress to disseminated disease, spreading to the CNS, bone, genitourinary tract, and skin. Primary cutaneous cryptococcosis from traumatic inoculation of the fungus is rare [83, 84].

Clinical Presentation

In immunocompetent hosts the infection is usually limited to the lungs, with minimal or no symptoms [85].

Skin has also been identified as a portal of entry of cryptococci. However, cutaneous lesions
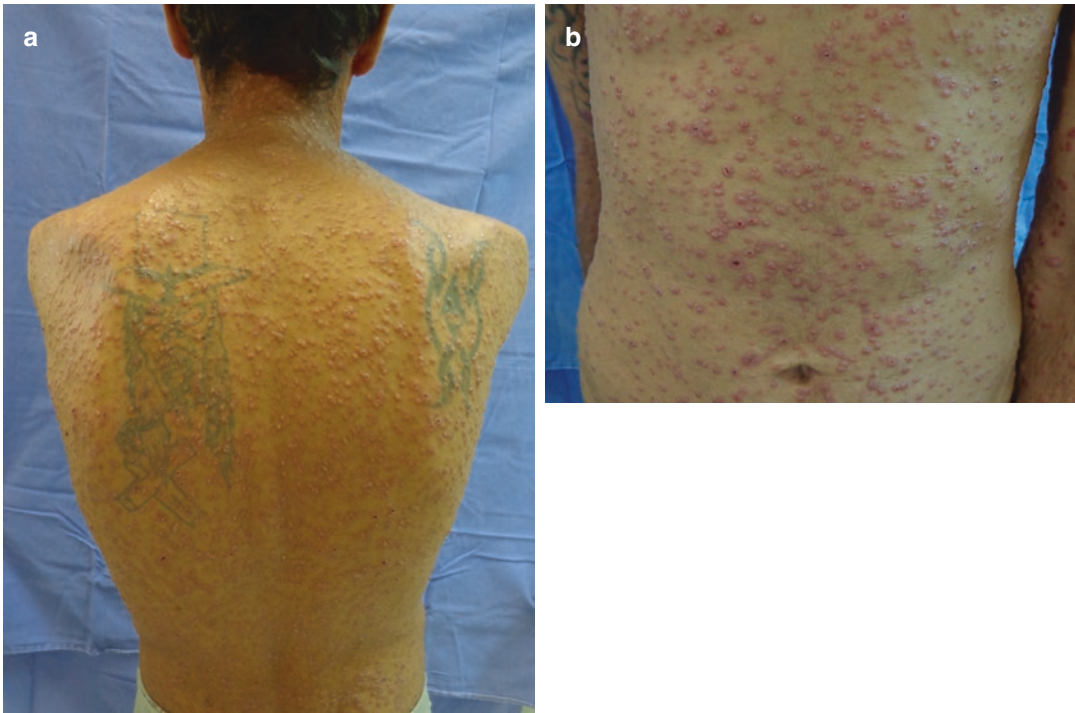
Fig. 11.25 (**a**, **b**) Cryptococcosis: disseminated molluscum-like lesions in an HIV-positive patient

largely represent hematogenous dissemination, involving mainly the scalp and the face. They present usually as acneiform lesions, but other presentations include nodules, ulcers, cellulitis, subcutaneous abscesses, pseudofolliculitis, and keloid-like or molluscum contagiosum-like lesions (Fig. 11.25a, b) [83, 86].

Complementary Examinations

Histopathologic analysis reveals microorganisms that are PAS-positive, presenting budding yeast cells with capsules, 2–20 mm in diameter. The fungi stain with Masson–Fontana and their capsule stains with Alcian blue and mucicarmine [83, 87].

Latex agglutination (LA) and ELISA have overall sensitivity and specificity of 93–100% and 93–98%, respectively. However, they are expensive and require a cold chain and significant technical expertise. Lateral flow immunoassay for the detection of CrAg (LFA CrAg) is a newly developed test that is sensitive and

specific, and simple to perform without field equipment, with results available in 10–15 min [85, 87].

Diagnosis

> **Box 11.19 Diagnosis of Cryptococcosis**
> Clinical presentation, diagnostic methods including microscopy and culture of fluids and/or tissues, histopathology, and detection of cryptococcal antigen (CrAg) by using either LA or ELISA in serum and cerebrospinal fluid [85, 87].

Differential Diagnosis

It is important to differentiate from other fungal infections caused by dimorphic fungi, such as histoplasmosis, coccidioidomycosis, and blastomycosis [83].

Therapeutic Approach

The treatment of disseminated disease/meningo-encephalitis consists of [85]:

- Induction phase: deoxycholate amphotericin B (AmB) 0.7–1.0 mg/kg (or liposomal AmB 3–4 mg/kg) intravenously, daily, plus flucytosine 100 mg/kg orally, divided into four doses for 2 weeks in HIV-positive or SOT patients, extending for at least 4 weeks in others
- Consolidation phase: oral fluconazole 400 mg daily for 8 weeks in HIV-positive, 400–800 mg daily in SOT, 800 mg daily in other patients
- Maintenance in HIV-positive patients: oral fluconazole 200 mg daily for a minimum of 12 months and CD4 >100 cells/mm^3 and an undetectable viral load for 3 months
- Maintenance in SOT recipients: oral fluconazole 200–400 mg daily for 6–12 months
- Maintenance in other patients: oral fluconazole 200 mg daily for 6–12 months

Some researchers recommend prophylactic treatment for asymptomatic HIV-positive patients who are CrAg-positive, especially if CD4 count is <100 cells/mm^3, with fluconazole 400–800 mg daily for 2 weeks followed by fluconazole 400 mg daily for 8 weeks. This strategy aims to reduce treatment costs and mortality associated with cryptococcal meningitis [85].

Glossary

Anthropophilic (dermatophytes) Restricted to human hosts, produce a mild, chronic inflammation.

Cytokine Any of a class of immunoregulatory proteins such as interleukin or interferon that are secreted by cells, especially of the immune system.

Ectothrix A fungus that grows inside the shaft of a hair but produces a conspicuous external sheath of spores.

Endothrix Dermatophyte infections of the hair that invade the hair shaft and internalize in the hair cell.

Folliculitis Common skin condition whereby hair follicles become inflamed, usually caused by a bacterial or fungal infection.

Geophilic (dermatophytes) Usually recovered from the soil, occasionally infect humans and animals; they cause a marked inflammatory reaction.

Hyperkeratosis Hypertrophy of the corneous layer of the skin.

Hypha (plural form hyphae) Name of the long, individual pieces that comprise a mycelium, overall a fungus; often described as strings and thread-like filaments.

Keratinocyte The predominant cell type in the epidermis.

Kerion The most severe form of tinea capitis, characterized by an abscess-like deep infection of the scalp. Clinically it is seen a boggy, indurated, tumor-like mass that exudes pus.

Leukonychia White spotting, streaking, or discoloration of the fingernails.

Mycelium Mass of hyphae that forms the body of a multicellular fungus; it enables either sexual or asexual reproduction of fungi.

Onycholysis Spontaneous separation of the nail plate, usually starting at the distal free margin and progressing proximally; the nail plate is separated from the underlying and/or lateral supporting structures.

Onychodystrophy Widely used, yet rarely defined term; it describes any kind of irregular difference in the nail, apart from modifications in color (called nail dyschromia).

Spore Specialized cell of the fungus that can function as resting or dispersal propagules; each spore has the capacity to generate another individual of the species.

Zoophilic (dermatophyte) Found primarily in animals, it causes marked inflammatory reactions in humans who have contact with infected cats, dogs, cattle, horses, birds, or other animals.

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Parasitic and Protozoal Infections

12

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Key Points Summary

- Scabies is a skin infestation caused by *Sarcoptes scabiei* var. *humanus* that affects more than 130 million people worldwide; topical permethrin is more effective than oral ivermectin, topical crotamiton, and topical lindane for the treatment of scabies
- Head lice predominantly infest schoolchildren from any socioeconomic group, and *Pediculus humanus* var. *capitis* is a parasitic insect that infests the hair and neck regions
- Chagas disease is endemic to Latin America but has spread to other continents because of population mobility.
- Bed bugs inject anticoagulant, hyaluronidase, proteases, and kinins into the skin and feed from the extracted blood or by directly collecting blood from the capillaries. The skin reactions are induced by the injected substances, and their type depends on the patient's immunocompetence and previous exposure, which represents a delayed reaction
- The most common type of myiasis is cutaneous myiasis, which includes localized furuncular myiasis, creeping dermal myiasis (migratory), and wound and body cavity myiasis
- Larva migrans is caused by cats' and dogs' intestinal hookworms. Humans are not the final hosts, explaining why it is a self-limited disease. The disease is endemic in tropical climates
- Leishmaniasis is a group of diseases caused by protozoan parasites of the genus *Leishmania*, and the WHO ranks cutaneous leishmaniasis as a category 1 (severely neglected) emerging and uncontrolled disease.

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Arthropod Infections

Scabies

Epidemiology

Scabies is a skin infestation caused by *Sarcoptes scabiei* var. *humanus* that affects more than 130 million people worldwide, especially in developing countries [1], where it is associated with low socioeconomic status and domestic crowding [2].

Etiopathogenesis

S. scabiei var. *humanus* is a parasitic mite that is round [3], has eight legs, and burrows into the stratum corneum of the skin, causing intense itching [4]. Female species of these mites have a size of approximately 0.4 mm, lay four eggs per day, and burrow under the stratum corneum for 6 weeks before dying [5, 6]. These mites feed on the host's epidermal cells and plasma, and take only 2 weeks to transform from the egg to the adult phase [5].

Scabies is transmitted by direct skin-to-skin contact from an infested to a susceptible person [5] and is less frequently caused by fomites [7]. Eggs can stay alive at low temperatures for up to 10 days outside of the host [5], whereas scabies mites do not survive more than 2–3 days away from human skin [3].

There are three clinical types of scabies: classical or ordinary, nodular, and crusted. Ordinary scabies (OS) is the most common type of skin infestation and presents a protective response mediated by Th1 cells. Crusted scabies (CS) affects immunosuppressed patients, such as individuals with developmental disability and leprosy [5], and is associated with a nonprotective T-helper 2 (Th2) response, eosinophilia, and extremely high levels of immunoglobulin G4 and total and scabies-specific immunoglobulin E in human serum [4].

Clinical Presentation

During the first infection, symptoms appear after 14 days and for up to 2 months [3, 5]. In subsequent infections the incubation period is 2 days. The main symptom of OS is severe itching, especially at night. Small excoriated papules and pustules (<5 mm) are commonly observed between the fingers (Fig. 12.1) and on the wrists, elbows, shoulders, genitalia (Fig. 12.2), breasts, ankles, waist, buttocks, shoulder blades, and armpits [3, 5]. Small burrows ending in a papule or pustule are difficult to observe and correspond to the course of the mite in the epidermis [5]. One clue to the proper diagnosis is the presence of itching with or without skin lesions in other household

Fig. 12.1 Scabies. Erythematous papular and eroded lesions in the interdigital web spaces of the hand

Fig. 12.2 Scabies. Erythematous crusted papular lesions on the penile shaft

members. Infestations in the head region are uncommon, but this type of infection is frequent in infants and babies [5]. Moreover, an average of 10–15 mites tends to appear in cases of OS [6].

Nodular scabies occur in some late infections in the form of larger and itchy papules or small nodules on the buttocks, genitalia, groin, and axilla. These lesions are called postscabetic nodules and represent a developing immune reaction to mite allergens [5, 7]. Mites are rarely found [7], but the search for the burrows is important, since they indicate active infection. Nodular scabies can also be found after the treatment [5].

CS, also known as Norwegian scabies, is a superinfection of mites (thousands to millions) during which patients are highly contagious [5–7]. In many cases other household members are also affected, mostly with OS [5]. The same areas are affected, although lesions may be smaller or may not present an itchy sensation (because of immunosuppression or neurologic disability). In these cases, dry scales and crusts generally appear, especially on the face, dorsum of the fingers, wrists, and ears, and some nails present hyperkeratosis [3, 5].

Diagnosis
The diagnosis is clinical.

Complementary Examinations
Direct examinations can confirm this infection: after scratching the end of the burrow [3], the material should be mounted in potassium hydroxide and observed under a microscope to search for mites, eggs, or feces [3, 5, 7]. Dermoscopy reveals an image that is similar to vapor trails from jet planes, which represent the burrow, whereas a brown triangular structure in the papule corresponds to the mouth of the mite [8]. In the burrow ink test, the papule is first marked with ink and then removed with an alcohol pad. A positive result shows a dark, zigzagged line that can be viewed by the naked eye, which corresponds to the burrow [9].

Histologically, when mites, eggs, or scybala are not found, pink "pigtails" connected to the stratum corneum are clues that represent the hatched and empty egg [10].

Differential Diagnosis
Folliculitis, insect bites, impetigo, papular urticaria, tinea corporis, contact dermatitis, bullous pemphigoid, and pityriasis rosea are part of the differential diagnosis [11]. CS can be misdiagnosed as psoriasis, hyperkeratotic eczema, Darier disease, or ichthyosis [12].

Therapeutic Approach
Treatment should be given to the patient and all household members, regardless of the symptoms [3, 5]. Topical agents are the first line of treatment, and oral ivermectin is reserved for recurrent and difficult-to-treat cases, CS, and epidemics [5, 7].

Topical agents are highly effective and should be applied to a clean body [3], including all body areas, from the neck to the feet and toes. The period of time that these agents are in contact with the skin must be strictly respected and then completely washed off [3, 5, 6]. In addition,

when treating infants and the elderly, scabicides should also be applied to their entire head and neck regions, avoiding the eyes, mouth, and non-intact skin [3, 5]. All of the topical agents used in a single application must be repeated 7–14 days after the first treatment [5].

Because the symptoms of scabies are caused by a hypersensitive reaction to mites and their feces, itching may continue for several weeks after treatment, even if all mites and eggs are killed. If itching persists for more than 4 weeks after treatment, or if new burrows or papules/pustules continue to appear, retreatment is necessary [3].

A systematic review of the literature [13] showed that topical permethrin is more effective than oral ivermectin, topical crotamiton, and topical lindane for the treatment of scabies, making permethrin the drug of choice [3]. It has also been proved to be safe in pregnant and lactating woman [5].

For CS, oral and topical agents should be used together [3]. Oral ivermectin (200 μg/kg/dose) should be taken with food and, depending on the severity of the infection, must be taken in three doses (approximately days 1, 2, and 8); five doses (approximately days 1, 2, 8, 9, and 15); or seven doses (approximately days 1, 2, 8, 9, 15, 22, and 29) [3]. Topical permethrin should be administered every 2–3 days for 1–2 weeks [3]. Keratolytic agents must be used to help the penetration of permethrin [3]. Patients must be isolated until both therapies are completed, providers must use gloves, and close contacts must be treated [6].

Demodicosis

Epidemiology

Demodex folliculorum and *Demodex brevis* are mites that are part of the human skin microbiota and inhabit the pilosebaceous unit of the face [14]. Demodecidosis, or demodicosis, is a pilosebaceous unit disease caused by human *Demodex* spp. mites, predominantly involving the face and head regions [15]. There are two types of demodicosis: primary and secondary. The former is more common in patients over 40 years of age, while the latter occurs earlier in life [16].

Etiopathogenesis

The symbiosis among humans, human *Demodex* mites, and the pathogenesis of demodicosis are still unclear [17]. A pathogenic role occurs when *Demodex* sp. penetrates the dermis, which is quite rare, or when it multiplies and its density is high (>5 mites/cm^2), which tends to occur more frequently [18].

Clinical Presentation

The diagnostic criteria for primary demodicosis include: (1) the absence of pre-existing or concurrent inflammatory dermatoses (acne, rosacea, or perioral dermatitis); (2) an increase in mite colonization; and (3) the control of the disease only after treatment with topical or systemic acaricides but not with antibiotics [16]. Clinically, the lesions involve periorificial sites of the face, have an asymmetric distribution and irregular shape, are bound by follicles, and are asymptomatic or mildly itchy [16]. Many definitions of the clinical presentation of primary demodicosis have been reported in the literature. Chen and Plewig [16], for example, proposed a didactic nomenclature for this condition (Table 12.1).

In secondary demodicosis, skin lesions have increased the density of mites and are associated with other concurrent skin or systemic diseases

Table 12.1 Primary human demodicosis: proposed classification and nomenclature

Proposed nomenclature	Definition and clinical manifestations
Spinulate demodicosis	Discrete fine, whitish to yellowish, spiky, changes involving sebaceous hair follicles, with or without faint erythema and little inflammation
Papulopustular demodicosis, perioral demodicosis, periorbital demodicosis, periauricular demodicosis	Papulopustules mostly involving the face (predilection for perioral, periorbital, and periauricular regions), in patients without (primary form) or with pre-existing inflammatory dermatoses (secondary form)
Nodulocystic/conglobate demodicosis	Intense immune reaction with massive follicular and perifollicular inflammatory infiltrates caused by *Demodex* proliferation, pus accumulation, and suppurative succulent changes

Adapted from Chen et al. [16]

(usually human immunodeficiency virus [HIV] and leukemia) or the use of topical (corticosteroids/calcineurin inhibitors) or systemic immunosuppressants [16]. Lesions have diffuse facial or truncal distribution and present greater inflammation [16]. *Demodex* spp. cause blepharitis, meibomian gland dysfunction, recurrent chalazia, and refractory keratoconjunctivitis [16, 19].

Diagnosis

The gold-standard diagnostic tool is a standardized skin surface biopsy, which should show >5 mites/cm^2 in demodicosis [16]. A noninvasive examination can also be performed whereby a drop of cyanocrylic adhesive is placed on a microscope slide, applying the adhesive-bearing surface of the slide to the skin and removing it gently after it is dry. On the other side of the slide, a waterproof draw of 1 cm^2 must be made. After its removal from the skin, the sample is clarified with two to three drops of immersion oil, covered with a coverslip, and observed under a microscope at standard magnification (×40, ×100) [20].

Differential Diagnosis

Perioral dermatitis, rosacea, folliculitis, and acne [17].

Therapeutic Approach

The treatment of human demodicosis is based on case reports and considers the same standard treatment as that applied for scabies [21]. However, evidence of the efficacy of these acaricides in the treatment of demodicosis is quite limited [16], whereas a single dose of ivermectin (200 µg/kg body weight) has been proved effective in the treatment of demodicosis [21]. Concurrent diseases in secondary demodicosis must also be treated [15].

Insect Infections

Head Lice

Epidemiology

Head lice, the most common type of lice, predominantly infest schoolchildren from any socioeconomic group [22].

Etiopathogenesis

Pediculus humanus var. *capitis* is a parasitic insect that infests the hair and neck regions. Adults feed on human blood and lay eggs in the base of hair shafts. They do not hop or fly, but rather crawl. Their main form of transmission is by direct contact with the hair of an infested person; pets do not transmit these parasites. Indirect transmission (combs, brushes, towels, hats, clothes) is less common, since the adult insects do not survive after 2 days if they fall off the child's head or their nits cannot hatch at temperatures lower than the human scalp [23].

Head lice have three forms: eggs (or nits), nymphs, and adults. Nits firmly attach to the hair shaft. They tend to have an oval shape, are very small, and take on a yellow, white, or hair-shaft color. Viable eggs are normally located 6 mm from the scalp and hatch in 8–9 days. Nymphs become adults 9–12 days after hatching. Adult head lice are 2–3 mm in size, have six legs, are grayish-white, and live up to 30 days in the head of the infested child. Adult lice and nits are found on the scalp, around the ears, and on the back of the neck. The former use their claws to firmly attach themselves to the scalp while the later firmly attach themselves to the hair shaft [23].

Clinical Presentation

Upon first infestation itching appears after 4 weeks, which is caused by sensitivity to the saliva from the head lice [24]. Erythematous papules, with a central excoriated point around the ears and the posterior portion of the neck, are common [24]. Secondary bacterial scalp infection may result from scratching and must direct attention to this diagnosis [22].

Diagnosis

The ability to see the nymph or adult head lice on the scalp or hair is one diagnosis. These lice move quickly and avoid light. The ability to see the nits attached to the hair shaft (Fig. 12.3) suggests the diagnosis of head lice but does not confirm it [23, 25].

Differential Diagnosis

Nits can be mistaken for black and white piedra, dandruff, hair casts (which are easily moveable while nits are not), hairspray droplets, monilethrix, and trichorrhexis nodosa [25].

Fig. 12.3 Head lice. Nits firmly attached to the hair shaft

Therapeutic Approach

Some pediculicides have an ovicidal effect. For pediculicides that are weakly ovicidal or nonovicidal, retreatment is necessary. For those that are strongly ovicidal, retreatment is recommended only if live lice are found several days after treatment [23].

Pyrethrines, extracted from chrysanthemum flowers, are neurotoxic to lice, since they connect themselves to the voltage-gated sodium channels, keeping them open and leading to spastic paralysis [26, 27]; however, they are associated with low toxicity to mammals. The shampoo or mousse must be applied to dry hair, maintained for 10 min, and rinsed off. Retreatment is necessary between 9 and 10 days [23, 24].

Permethrins are synthetic pyrethroids. Instructions for use are the same as for pyrethrines, but these must be applied to damp hair [23, 24].

A 5% benzyl alcohol lotion must be applied to dry hair for 10 min to saturate the scalp and the entire length of the hair, and then rinsed off. Retreatment should be performed 9 days after the first treatment [23, 24].

Malathion at 0.5% is an insecticide that, when ingested by lice, is converted into its active metabolite, malaoxon, a cholinesterase inhibitor that causes spastic paralysis and kills lice [27, 28]. This insecticide is considered safe because, when used topically, malathion is metabolized into its inactive metabolites rather than into its active metabolites, and these inactive metabolites can be excreted by the kidneys [28]. It must be applied to dry hair and left to air dry for 8–12 h, then washed off. Caution must be exercised while the product is in use because the solution is inflammable (78% isopropyl alcohol): the hair must dry naturally; there should be no smoke near the patient; hair dryers, curling irons, and flat irons must not be used. This treatment has been proved to produce good ovicidal activity [23].

Ivermectin at 0.5% increases the chloride ion permeability of muscle cells, resulting in the paralysis and death of the lice. This must be applied to dry hair and scalp and left for 10 min before rinsing off. Only one application is necessary because, when the nits hatch, nymphs are not able to feed because of pharyngeal muscle paralysis [26, 29]

Systemic ivermectin is an off-label treatment for head lice. A single oral dose of 200 µg/kg body weight should be applied and repeated after 10 days [26].

Spinosad at 0.9% is derived from the fermentation of the *Saccharopolyspora spinosa* bacteria [24]. Its mechanism of action is not completely known, but it appears to indirectly interfere with a subset of nicotinic acetylcholine receptors, as

well as with γ-aminobutyric acid gated chloride channels, leading to motor neuron excitation and involuntary muscle contraction with paralysis [30]. This solution must be kept in dry hair for 10 min and then rinsed off. A second treatment is necessary after 7 days only if live lice can still be seen [30]. This medication is classified as pregnancy category B [30].

The widespread use of insecticides for this treatment has led to the emergence of resistance to the pediculicides in many parts of the world. Three point mutations in the voltage-gated sodium channels are associated with permethrin-resistant phenotypes, which were suggested to be responsible for kdr-type resistance. In the United Kingdom, where malathion has been used for a longer period of time, resistant cases were proposed to be linked to modified acetylcholinesterase [27].

Since by the time the infestation is diagnosed the child has been infected for at least 1 month or more, and considering that the risk of transmission at school to other children is small, the child must remain in class [24]. Close contact should be checked and the infested child should be treated at the same time [23].

Body Lice

Epidemiology

Pediculus humanus var. *corporis* is an ectoparasite that only infests humans and is usually found in the homeless, refugees, victims of war, or natural disasters, since it is associated with poverty, crowded places, and poor hygiene [31]. The infestation can be transmitted either by direct contact with the infested person or by indirect contact (clothes, beds, and bath clothing) [32]. The ectoparasite transmits diseases such as epidemic typhus, trench fever, endocarditis by *Bartonella quintana*, and relapsing fever [31, 33].

Etiopathogenesis

The adult parasites are 2–4 mm in size; other than their length, it is not possible to distinguish them from head lice. The insects attach themselves to hair shafts of the body to feed on blood [33], and lay their eggs in hair shafts and in the seams of clothing [32, 33]. The eggs hatch in about 7 days [32]. The nymphs mature into adult parasites in about 2 weeks [33] and live an average of 30 days [32].

Clinical Presentation

The infested patient presents intense pruritus, excoriation, rash stemming from reaction to the bite, secondary skin bacterial infection, and chronic lichenification [31, 34].

Diagnosis

The diagnosis is made by identifying body lice or eggs in the skin or in the seams of clothing [32–34].

Differential Diagnosis

Atopic dermatitis, contact dermatitis, viral exanthem, rash from medication, and scabies [32].

Therapeutic Approach

A body lice infestation is treated by improving the personal hygiene of the infested person, including assuring a regular (at least weekly) change of clean clothes. Clothing, bedding, and towels used by the infested person should be laundered using hot water (at least 54.5 °C) and machine dried using the hot cycle. The use of pediculicides is not necessary, but if chosen should follow the same instructions as those for the treatment of head lice [31].

Hemiptera Infestations

Triatomine Bug Infestations

Epidemiology

Triatomine bug, also called the kissing bug, reduviid bug, assassin bug, cone-nosed bug, and blood sucker, is an insect that transmits Chagas disease, caused by *Trypanosoma cruzi*, a protozoan parasite. This disease is endemic to Latin America but has spread to other continents because of population mobility. Estimates quote that 6–7 million people worldwide are infected,

and the insect can be found throughout the Americas [35]. *T. cruzi* can also be transmitted by the consumption of food contaminated with triatomine's feces or urine, blood transfusion, vertical transmission, organ transplants, and laboratory accidents. Since the 1990s, in Latin America there has been an important reduction in transmission by vectors, via vector control, and by blood transfusion, by means of compulsory blood screening in blood banks [35].

Etiopathogenesis

Triatomines are 10–30 mm in size; their wings rest on their back, the lateral portion of their abdomen is not covered by wings, and they have tiger-like stripes [36]. The insects are attracted by houselights [37]. Indoors, they live in cracks of substandard housing, pets' resting areas, in rodent infestation, and in and around beds. Outdoors, they live beneath porches, between rocks, under cement, in wood and brush piles, beneath bark, in rodent nests, in animal burrows, in outdoor dog houses, and in chicken coops [38].

Triatomines have nocturnal habits and feed on the blood of mammals (including humans), birds, and reptiles [38]. People become infected when they ingest *T. cruzi* from the blood of an infected mammal [37]. *T. cruzi* must be in the bug's feces to be transmitted. Triatomines frequently defecate while feeding [36–38] on a person who is sleeping. They produce painless feeding bites [36], and protozoa transmission occurs when feces are rubbed into the bite wound or into a mucous membrane, thus allowing the parasite to enter the body. However, it is important to note that not all triatomines are infected with *T. cruzi* [38].

Clinical Presentation

The incubation period of the acute disease is 1–2 weeks [39] and is marked by Romaña's sign, a unilateral periocular swelling caused by a conjunctival edema due to contamination from triatomine feces [37]. Chagoma is a mild swelling at the site of the parasite's inoculation. About 30–40% of the patients develop this chronic disease after 10–30 years with cardiac and digestive infections [39].

Even though the triatomine may not be infected, antigens from saliva can induce allergic reactions [36–38]. Initially the lesions are pruriginous and made up of erythematous papules with a central punctum that emerges 24 h after the bite; with multiple exposures, reactions may appear as hemorrhagic nodules, bullae, diffuse urticaria, erythema multiforme, and, more rarely, anaphylactic shock [37].

Chagoma and Romaña's sign have less pruritus and last longer (weeks) than do allergic reactions (hours to several days) [37]. Romaña's sign can occur without the transmission of *T. cruzi* [37].

Diagnosis

During the acute phase of Chagas disease, diagnosis is made by the identification of the parasites in a blood smear by microscopic examination or molecular study. In chronic stages, at least two different serologic tests are necessary [38].

Differential Diagnosis

Romaña's sign must be differentiated from allergic reactions to insect bites or stings, pollen, aspirin, or foreign bodies [37].

Therapeutic Approach

The treatment of the acute phase of Chagas disease is curative with benznidazole or nifurtimox [38]. In case reports, allergic reactions were managed with oral prednisone and antihistamines. The treatment of anaphylactic reaction was performed in the emergency room [37].

Bed Bugs

Epidemiology

Bed bugs belong to the Cimicidae family and are wingless ectoparasites that feed on the blood of humans, mammals, and birds [40], but do not transmit disease [41].

Bed bugs have a worldwide distribution and are common in developing countries, but have recently spread to developed countries because of international travel and immigration. Their infestation is not associated with poor hygiene [41, 42], as they have even been found in five-star

hotels and resorts, since they can be transported in bags and furniture [41]. The two species usually responsible for human infestation are *Cimex lectularius* (worldwide distribution) and *Cimex hemipterus* (tropical climates) [40].

Etiopathogenesis
Bed bugs usually hide 1–2 m from the victim in crevices, bed cracks, seams of mattresses, box springs, headboards, loose wallpaper, and behind hanging pictures where they avoid daylight [43]. They feed from blood during the night, especially before dawn [40, 42].

The eggs are deposited in crevices and hatch 4–12 days later [41]. Nymphs become adults after the fifth molting. The adults are 5–8 mm in size and can easily be seen; the parasites have three pairs of legs, are flat and reddish-brown [42, 43], live from 6 to 12 months, and can survive up to 1 year without feeding [41, 43]. They can also produce a pungent odor [40].

Bed bugs inject anticoagulant, hyaluronidase, proteases, and kinins into the skin and feed from the extracted blood or by directly collecting blood from the capillaries. The skin reactions are induced by the injected substances, and their type depends on the patient's immunocompetence and previous exposure, which represents a delayed reaction [40].

Clinical Presentation
Some patients are asymptomatic. The signs and symptoms of the bite may appear the next day or up to 14 days after the initial bite [41]. Lesions are found in exposed areas, such as the face, neck, hands, and arms. They can be distributed randomly or placed in linear disposition ("breakfast, lunch, and dinner") (Fig. 12.4) [41, 42]. Asymptomatic macules, hemorrhagic puncture, erythematous wheals centered by a punctum, urticarial papules, or bullous lesions at the site of the bite associated with pruritus are to be expected. Anxiety, lack of sleep, and anaphylaxis, though rare, can also occur [40].

Diagnosis
The inspection of the possible infested area is necessary to ensure a proper diagnosis. Signs that

Fig. 12.4 Bed bug. A linear pattern of papular erythematous lesions on the leg

must be searched for include: the bed bugs' exoskeletons after molting; bed bugs in the fold of mattresses and sheets; rusty-colored blood spots resulting from the blood-filled fecal material that they excrete on the mattress or in the furniture; and the pungent odor they produce [41]. A quick search during the night with a flashlight (especially at 4:00 am) may aid in identifying these parasites [42].

Differential Diagnosis
Bites of fleas, parasitic mites, scabies (usually affects covered skin), dermatitis herpetiformis [42], and papulovesicular dermatitis of Gianotti–Crosti [40].

Therapeutic Approach
Bites and pruritus can be treated with systemic antihistaminic or topical corticosteroids and good hygiene to prevent any secondary infection of the skin. The infestation must be managed by a pest control professional [42]. The best way to prevent this infestation is to inspect the location for

signs of parasite. When sleeping in hotels or other unfamiliar places, a prudent approach is to check the premises for bed bugs and their excreta: mattress cords, crevices, cracks, headboards, and so forth [43].

Dipterous Larvae Infestations

Myiasis

Myiasis (from the Greek word for "fly," *myia*) refers to an infestation of human tissue by fly larvae, within the Diptera arthropod order, which feed on living tissue, body fluids, or ingested foods. The most common type of myiasis is cutaneous myiasis, which includes localized furuncular myiasis, typically caused by *Dermatobia hominis*, *Cordylobia anthropophaga*, *Wohlfahrtia vigil*, and *Cuterebra* spp.; creeping dermal myiasis (migratory) caused by *Gasterophilus* spp. and *Hypoderma* spp.; and wound and body cavity myiasis caused by screwworm flies *Cochliomyia hominivorax*, *Chrysomya bezziana*, and *Wohlfahrtia magnifica* [44, 45]. Less common types of infestation include enteric, ophthalmic, nasopharyngeal, auricular, oral, and urogenital myiasis [46].

Follicular Myiasis

Epidemiology

Myiasis is a worldwide infestation with seasonal variation; its incidence is higher in the tropics and subtropics of Africa and the Americas. The Tumbu fly, *C. anthropophaga*, is the most common vector for myiasis in Africa, while the human botfly, *D. hominis*, is endemic throughout Central and South America [45]. The *Cordylobia* genus also contains two less common species (*Cordylobia ruandae* and *Cordylobia rodhaini*). Infection by *C. rodhaini* (Lund's fly) is less common [47]. Autochthonous furuncular myiasis caused by accidental infestation of humans by larvae of flies belonging to the genus *Cuterebra*, commonly known as "rabbit botflies" or "rodent

botflies," has been reported in the United States [48]. Cutaneous myiasis is usually an uncomplicated and self-limiting disease.

Etiopathogenesis

D. hominis larvae are indirectly transmitted to vertebrate animals by blood-feeding arthropods such as mosquitoes, on whose abdomens the adult female botfly has deposited her eggs (means of transportation known as phoresy). When the blood-feeding arthropod takes a blood meal from a warm-blooded animal, the change in temperature causes the botfly eggs to hatch. The larvae painlessly enter the vertebrate host through a hair follicle or the bite site or by directly burrowing into the skin. Over the next 4–18 weeks, the larva grows by eating the flesh of its host and becomes pyriform to ovoid in shape until it reaches full development at lengths of 15–20 mm. At maturity, the larva emerges from the wound and falls to the soil where it pupates to form flies in 2–4 weeks [45, 46].

Clinical Presentation

In humans, the skin lesion starts within 24 h of penetration as a pruritic erythematous papule that gradually enlarges and develops into a furuncle. Typically, the center of the lesion has a central punctum (Fig. 12.5) from which serosanguinous fluid may be discharged and through which the larva breathes; the movement of the larva may be noticed by the patient. Lymphangitis and regional lymphadenopathy may be noted [45, 46].

Fig. 12.5 Follicular myiasis. Furuncular lesion on the back

Diagnosis

Diagnosis is typically made by identifying the fly larvae or maggots. The exact type of species can be difficult to determine by examination. A leucogram may show leukocytosis and eosinophilia. Histopathologic examination is not necessary, but if performed cutaneous biopsy findings include an ulcerated epidermis with an inflammatory infiltrate of neutrophils, lymphocytes, giant cells, mast cells, plasma cells, and eosinophils that occur in stages. The larvae can be seen in cross-section. Ultrasonography can also be very useful in establishing the diagnosis and determining the size of the larvae [46, 48].

Differential Diagnosis

Abscess, cellulitis, exaggerated arthropod reaction, furunculosis, ruptured epidermoid cyst, and tungiasis [45, 46].

Therapeutic Approach

Treatment for myiasis can be conservative or surgical. Noninvasive approaches include the application of heavy oil, occlusive ointment, pork fat, or bacon strips over the central punctum to interrupt the larva's respiration and forcing it to migrate to the surface of the lesion, from which it can be removed easily. Surgical treatment consists of the mechanical removal of the larva, which may be performed by the use of local anesthesia with lidocaine followed by primary wound closure. Lidocaine can also be injected forcibly into the base of the lesion in an attempt to create enough fluid pressure to extrude the larva out of the punctum [45, 46].

An alternative treatment for all types of myiasis is oral ivermectin or topical ivermectin (1% solution), which has proved especially helpful with oral and orbital myiasis [45].

Creeping Myiasis

Migratory myiasis, also called "creeping dermal myiasis," is caused by flies belonging to the *Gastrophilus* and *Hypoderma* genera. The first are usually gastrointestinal (*Gasterophilus intestinalis*) or nasal (*Gasterophilus nasalis*) parasites from horses; human myiasis caused by horse botflies (*Gastrophilus* species) is very rare. In humans the larvae initially produce a papular lesion, which resembles those seen in cases of furuncular myiasis, and then burrow and wander intradermally, creating narrow, tortuous, erythematous, and linear lesions with intense pruritus. This form of myiasis resembles cutaneous larva migrans [49].

The larvae of *Hypoderma* species are parasites from deer, cattle, and horses. Humans are abnormal hosts in which the parasite is unable to fully mature. In humans, the larvae migrate rapidly and erratically through the subcutaneous tissues, producing intermittent, painful swelling over months. The larvae may emerge spontaneously from the furuncles or die within the tissues. In rare cases the larvae are seen to invade the orbit, pharyngeal region, and spinal canal [49].

Wound Myiasis

Wound myiasis occurs when female flies deposit the eggs near poorly managed wounds, and the larvae feed on necrotic tissue. The majority (85–90%) of cases are caused by fly larvae belonging to the Calliphoridae family. The diagnosis is obvious when larvae are visible on the surface within or around the wound (Fig. 12.6) and more difficult when they have burrowed beneath the surface. Wound myiasis requires debridement with irrigation to eliminate the larvae from the wound or surgical removal [50].

Fig. 12.6 Wound myiasis. A traumatic ulcer from where larvae were removed

Helminthic Infections

Hookworm-Related Cutaneous Larva Migrans

Epidemiology

Hookworm-related cutaneous larva migrans is caused by cats' and dogs' intestinal hookworms *Ancylostoma braziliense*, *Ancylostoma caninum*, and *Uncinaria stenocephala*. Humans are not the final hosts, explaining why it is a self-limited disease. The disease is endemic in tropical climates; in developed countries this parasite normally only affects tourists returning from endemic areas [51].

Etiopathogenesis

When the infected animals defecate in the sand or soil, the eggs are eliminated through feces. In the environment they hatch and larvae should, under appropriate conditions (moisture, warmth, and shade), molt into the third stage, when human skin can be infected during direct contact with the contaminated soil or sand, into which the larvae actively penetrate. Since humans are not the definitive hosts, the larvae migrate within the epidermis and do not complete the hookworm's life cycle; therefore, the larva dies after 5–6 weeks [51].

Clinical Presentation

Feet, buttocks, and thighs are usually the most commonly affected parts, as they come into contact with contaminated soil. Intense pruritus starts shortly after the larval penetration within the epidermis, which seems to be caused by substances released by the larvae that irritate itching fibers [52]. A reddish papule indicates the site of penetration. After a variable period of time a serpiginous, erythematous, and elevated plaque is visible (Fig. 12.7) [53] and moves from one location to another, as the larva migrates aimlessly within the epidermis until it dies. Lesions are extremely itchy and bacterial secondary infection may occur [51]. Papular lesions may occur (Fig. 12.8); vesicobullous lesions have also been described in prior case reports, whose pathophysiology is still unknown [54].

Folliculitis is an uncommon manifestation associated with a serpiginous track and resistance to treatment [55].

Fig. 12.7 Cutaneous larva migrans. Erythematous, single-track linear and serpiginous lesions

Fig. 12.8 Cutaneous larva migrans. Papular erythematous lesions on the face

Diagnosis

The diagnosis is clinical [51–53].

Differential Diagnosis

Scabies, loiasis, myiasis, cercarial dermatitis, tinea corporis, and contact dermatitis [53]. Larva currens affects the thighs, perianal

Table 12.2 Treatment for cutaneous larva migrans

Drug	Adult dose	Pediatric dose
Albendazole	400 mg/day orally for 3–7 days	Children >2 years of age: 400 mg/day orally for 3 days
		Contraindicated for children <2 years of age
Ivermectin	200 μg/kg body weight orally in a single dose	Children >15 kg body weight: 200 μg/kg/day orally in a single dose
	Contraindicated in pregnant and lactating women	Contraindicated in children <15 kg body weight

Source: Centers for Disease Control and Prevention [51]

region, and trunk; larvae migrate faster than animals' hookworms, and lesions last for just a few hours [56].

Therapeutic Approach

Freezing the lesions is not recommended; this treatment has proved ineffective, since the larva is usually located beyond the visible track and causes pain, ulcers, and blisters [55].

A 10–15% topical thiabendazole solution applied three times daily for 1 week has the advantage of the absence of systemic side effects. Its disadvantages include a limited effect against multiple lesions and folliculitis and necessity of its application several times a day [55].

Treatment with systemic albendazole or ivermectin is curative. In cases of folliculitis, additional doses may be necessary. Children under 2 years of age or under 15 kg body weight may be treated with topical preparations. Albendazole is a pregnancy category C agent and should only be prescribed if the potential benefit justifies the potential risk to the fetus [51]. These drugs are curative choices. Systemic thiabendazole is associated with several side effects; therefore, its use is not recommended [52]. Table 12.2 shows the different dosage regimens.

Protozoal Infections

Leishmaniasis

Epidemiology

Leishmaniases are a group of diseases caused by protozoan parasites of the genus *Leishmania*. The disease is transmitted to humans by the bite of infected female sandflies (*Phlebotomus* or *Lutzomyia* spp.). The clinical manifestations depend on the extent of the involvement and can be broadly classified as cutaneous leishmaniasis (CL), the most common variety, visceral leishmaniasis (VL) or kala-azar, the most deadly parasitic infection after malaria, and mucocutaneous leishmaniasis (MCL), with its disfigurement potential [57].

The World Health Organization (WHO) estimates the global incidence of VL as 300,000 cases with over 20,000 deaths annually, and 1 million cases of CL have been reported in the past 5 years [58]. The WHO ranks CL as a category 1 (severely neglected) emerging and uncontrolled disease [59] and has created the slogan "Small bite, big threat" to highlight the increasing burden of vector-borne diseases [60, 61].

Globally, human leishmaniases are endemic in 98 countries and three territories, with the exception of Antarctica and Australia [62]. VL exists in the eastern and western hemisphere and more than 90% of the cases are reported in poverty-stricken countries such as India, Bangladesh, Sudan, Ethiopia, and Brazil, with a mortality rate of 10–20% [63]. CL is more widely distributed, with about one-third of the cases occurring in the Americas, the Mediterranean Basin, and Western Asia from the Middle East to Central Asia. The ten countries with the highest estimated case counts (Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, North Sudan, Costa Rica and Peru) together account for 70–75% of the estimated incidence of CL worldwide [62]. New World CL extends from Central and South Texas throughout Latin America, with the exception of Chile and Uruguay. Nearly 90% of MCL cases are from Bolivia, Brazil, and Peru [58].

Historically regarded as a disorder of tropical and subtropical regions, leishmaniasis has dramatically

expanded its boundaries. This change in the epidemiologic profile is largely favored by climate changes, increased touristic and work-related traveling, uncontrolled urbanization, deforestation, and massive migration caused by civil conflict and war [64–67].

Etiopathogenesis

Leishmaniasis is caused by different protozoa of the genus [68]. All species involved in Old World leishmaniasis are distinct from those found in New World leishmaniasis, with the exception of *Leishmania infantum*, which has been proved to be indistinguishable from *Leishmania chagasi* [69]. Two morphologic forms are recognized in the lifecycle of *Leishmania*: an extracellular, motile, 15–20 μm long, flagellated promastigote (leptomonad form) found in the invertebrate host, and an obligate intracellular, nonmotile, 3–5 μm long, nonflagellated amastigote (leishmanial form) observed inside the macrophages of the mammalian host [79]. During a sandfly's blood meal on an infected host, ingested amastigotes are retransformed back in promastigotes into the insect gut, multiply, and are ready to be injected in silvatic or human hosts. Once in the mammalian host, promastigotes are captured by macrophages and turned into amastigotes. Both amastigote and promastigote forms multiply by binary fission in the vertebrate host's macrophages or in the sandfly digestive tube, respectively [70].

A wide range of animals, with remarkable geographic variations, can serve as vertebrate hosts, such as rodents, marsupials, dogs, bats, baboons, leopards, sloths, foxes, and hyenas [62]. New World leishmaniasis is fundamentally a zoonosis; i.e., parasites causing the infection are those from wild animals. Whether infected humans can be a source of protozoa for sandflies is still a matter of dispute [61]. Old World leishmaniasis occurs as a zoonosis and, occasionally, as an anthroponosis (*Leishmania tropica*).

In natural silvatic hosts, the disease is usually benign or unapparent. Peridomiciliary animals such as horses, mules, and dogs may eventually present with lesions demonstrating that they are, like humans, unnatural hosts to *Leishmania*. Most of the reported cases are caused by *Leishmania braziliensis* [61].

Genomic differences acquired during the evolution of *Leishmania* may well explain the preference of some species to target the skin or invade visceral organs [71]. *L. tropica*, *Leishmania major*, and *Leishmania aethiopica* cause skin lesions in the Old World, while infection by *Leishmania donovani* results in visceralization and *L. infantum* can promote both visceral and skin involvement. Anergic diffuse CL (ADCL) has been associated with infection caused by species of the *Mexicana* complex (*Leishmania amazonensis*, *Leishmania mexicana*, and *Leishmania pifanoi*) in the New World, and *L. aethiopica* in the Old World [61]. Mutilating, destructive MCL is observed only in New World and is related to *L. braziliensis*, *Leishmania guyanensis*, *Leishmania panamensis*, and *Leishmania peruviana* infection, whereas *L. aethiopica* may cause localized anatomic distortion because of oronasal lesions.

Murine models for CL have shown the key role of Th1 CD4+ cells. In brief, interacting with an antigen-presenting cell exposed to the parasites, CD4+ Th lymphocytes release interferon-γ which, in turn, activates the production of nitric oxide by macrophages, resulting in the killing of the amastigotes [72]. Localized, self-healing lesions have a predominant Th1 profile, while the Th2 profile is found in diffuse and nonhealing lesions. These immune responses also account for the diverse clinical manifestation of leishmaniasis [73].

Clinical Syndromes

Infection by *Leishmania* in humans produces a full spectrum of manifestations, ranging from asymptomatic to lethal. This fact is strikingly remarkable since leishmaniases are caused by morphologically similar organisms living in a single series of cells [74]. The resulting clinical

Fig. 12.9 Cutaneous leishmaniasis. An ulcer with slightly elevated and indurated borders with a *reddish* and crusted base

presentation depends on a complex interplay involving infecting species, vector, immune response mounted by the host, nutritional status, age, inoculation site, and genetic background [64, 75]. Three clinical syndromes (VL, CL, and MCL) and two distinct entities (ADCL and post-kala-azar dermal leishmaniasis, PKDL) are recognized. VL clinical manifestations, diagnosis, and therapeutic approaches are not discussed in this chapter.

Cutaneous Leishmaniasis

CL is the most common and the least severe form of the disease. It is characterized by one or more lesions that develop from weeks to months after the bite and favor exposed areas (face, upper and lower limbs). The initial lesion, a patchy erythema with variable induration, is quite nonspecific and rarely seen by the examining physician. From this starting point the disease may run a variable course, ranging from spontaneous healing to progression to papules, nodules, ulcers, and mucous membrane involvement [76]. Enlargement of lymph nodes adjacent to skin lesions may be occasionally observed.

The typical ulcer is rounded, crater-like, with a raised (framing) border (Fig. 12.9). As it is

Fig. 12.10 Cutaneous leishmaniasis. Keratocanthoma-like tumoral lesion

observed in both Old World and New World forms, the causative species may not be inferred by the appearance of the lesion [61].

The polymorphous status of cutaneous lesions is expressed by a vast array of adjectives employed in their description: impetigoid, lupoid, verrucous, lichenoid, framboesiform (raspberry-like), tumoral, vegetative, verrucous, and so forth (Figs. 12.10, 12.11, and 12.12). Of note, all lesions in CL share the common feature of being asymptomatic.

Fig. 12.11 Cutaneous
leishmaniasis.
Sporotrichoid-nodular
form of leishmaniasis on
the lower leg

Fig. 12.11 Cutaneous leishmaniasis. Sporotrichoid-nodular form of leishmaniasis on the lower leg

Fig. 12.12 Cutaneous leishmaniasis. Vegetating knee ulcer

Mucocutaneous Leishmaniasis

Although MCL has been attributed, in rare instances, to *L. guyanensis* and *L. panamensis*, the vast majority of cases in the New World are caused by *L. braziliensis* [61]. Mucosal lesions may result from the extension of a contiguous skin lesion (Fig. 12.13) or by hematogenic or lymphatic dissemination (Fig. 12.14). Early signs include nasal congestion, bleeding, and hoarseness. Rapid invasion of the nasal mucosa with mutilation may ensue. It is not clearly understood why some patients infected by *L. braziliensis* develop MCL while others remain with lesions restricted to the skin. Associated risk factors include incomplete or missing treatment of the primary CL, malnutrition, large and multiple lesions, male gender, and genetic background [64, 77].

Anergic Diffuse Cutaneous Leishmaniasis

Characteristically, multiple skin-colored, painless papules and nodules, with no tendency to ulcerate, appear on the face, ear, elbows, and knees and may slowly progress to involve the entire body surface and, eventually, mucous membranes. Colonic infiltration has been reported in patients with immune reconstitution inflammatory syndrome after initiation of highly active antiretroviral therapy [78]. The multiple nodules on the face are reminiscent of leonine

Fig. 12.13 Mucocutaneous leishmaniasis. Nasal erythema and edema, ulceration, and bleeding of the nasal septum as well as erythematous infiltration of the skin around the nose

Fig. 12.14 Mucosal leishmaniasis. Granulomatous gingival enlargement

facies, hence the term lepromatous leishmaniasis. ADCL has also been simply referred to as diffuse or disseminated leishmaniasis. These are clearly misnomers given that immunologically competent patients may present perfectly curable multiple lesions [61]. Therefore the term anergic, which denotes the defective cell-mediated response (a Montenegro skin test is always negative), the hallmark of ADCL, should be compulsory.

The lesions contain an enormous number of large-sized parasites, and treatment resistance is common. New World ADCL is caused by *L.*

amazonensis, *L. mexicana*, and *L. pifanoi* (all belonging to the *Mexicana* complex) while *L. aethiopica* is the offending species in Old World ADCL.

Diagnosis

The diagnosis is based on clinical features, epidemiologic data, and laboratory tests. As with any other infectious disease, the diagnosis can only be formally confirmed by the demonstration of the parasites. The most effective and less expensive method is the identification of parasite by light microscopic examination of a stained specimen (Giemsa, Wright, or Feulgen stain) [80]. The edge of a recently appeared lesion is the site of choice to obtain tissue samples by scraping, biopsy, or needle aspiration. On light microscopy, the amastigotes within the cytoplasm of tissue macrophages are seen as pale-blue oval bodies measuring 2–3 μm in length and present a dark-blue nucleus and a deep red or violet rod-like paranuclear body called a kinetoplast (Fig. 12.15) [81]. ADCL is known for its abundance of parasites, whereas the chances of detection in CL and MCL are inversely proportional to the duration of the infection.
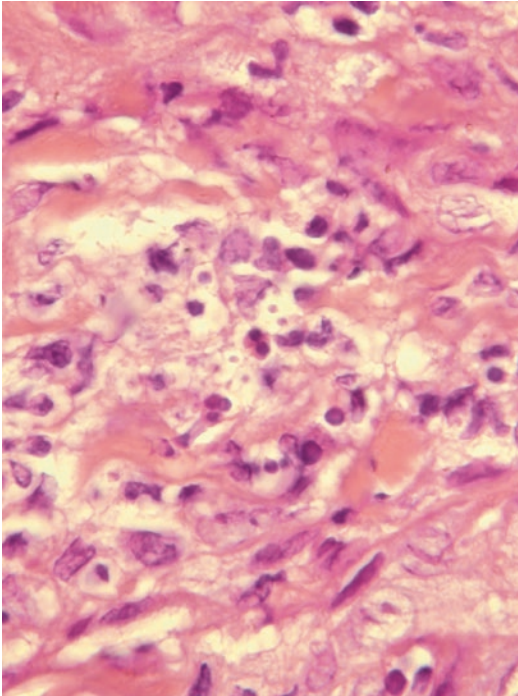
Fig. 12.15 Cutaneous leishmaniasis. Skin biopsy examination shows an inflammatory perivascular and interstitial infiltrate consisting of plasmocytes, lymphocytes, and vacuolated histiocytes which contained amastigotes (hematoxylin–eosin, ×40)

Complementary Examinations

Leishmania can be cultured in monophasic (Schneider's insect medium, M199, or Grace's medium) or diphasic media (Novy-McNeal Nicolle medium and Tobies medium). Cultures should not be discarded as negative before 4 weeks. Some strains will not grow in culture and require inoculation into susceptible animals, such as hamsters. Because of the prolonged time required to obtain results (7–9 months), animal inoculation is not employed in routine clinical practice.

The polymerase chain reaction (PCR), the most sensitive, specific, and fastest method currently available, is the best approach to diagnose leishmaniasis but requires adequate infrastructure and technically skilled operators [59, 82]. In cases where the parasite load is low, such as in long-standing cutaneous lesions, mucosal impairment, and immunosuppression, PCR is especially useful [83]. As an additional advantage, PCR can also identify *Leishmania* species. This may be relevant in areas where leishmaniasis is caused by different parasites with distinct treatment response [84].

Different evaluated PCR methods demonstrate superior sensitivity when compared with microscopy smear and in vitro cultures [85, 86]. However, the best diagnostic approach is the combination of different laboratory tests to increase detection sensitivity [87]. In an endemic area of CL due to *L. guyanensis* and *L. braziliensis*, the combination of skin smear, PCR, and histopathology increased diagnostic sensitivity to 94% [88].

Serologic assays are rarely used for CL and MCL because of the poor humoral response generated by the infection and, therefore, low sensitivity [89]. The Montenegro skin test, also known as the leishmanin test, is used to measure the cell-mediated immune response by injecting 0.1 ml of a phenol-killed preparation of *Leishmania* promastigotes in the anterior aspect of the forearm. After 48–72 h, the reaction is measured and an induration of 5 mm or more is considered positive. However, this test does not differentiate past exposure from active disease and may remain positive after cure [90]. Active PKDL and ADCL show a negative intradermal test.

The histopathologic findings of the skin specimen depend largely on the stage of development of the lesion, host response, and degree of cellular immunity [64]. A spectrum of features, similar to that observed in leprosy, can be found. The anergic pole shows abundant parasites in the cytoplasm of macrophages, no giant cell or ulceration, and little necrosis. The opposite hyperergic pole is tuberculoid, displays epithelioid cell granulomas, large Langerhans cells, and few or no detectable parasites. Between these stable poles a wide variety of histopathologic changes, such as hyperplasia, polycellular infiltrate, necrosis, ulceration, and healing can be observed [74].

Differential Diagnosis

Initial papules or crusted lesions should be differentiated from arthropod bites and impetigo. Buruli ulcer, stasis ulcer, and pyoderma gangrenosum should be included as differential diagnoses of ulcerated lesions, while the possibility of neoplastic

skin conditions (basal and squamous cell carcinoma, lymphoma) or sarcoidosis should be considered when verrucous, plaque, or nodular lesions are present. Sporotrichosis, North and South American blastomycosis, chromomycosis, leprosy and other mycobacterioses, botryomycosis, syphilis, myiasis, tungiasis, furuncle, ecthyma, and carbuncle may resemble CL. ADCL may be difficult to distinguish from lepromatous leprosy and lobomycosis.

Therapeutic Approach

There are multiple therapeutic options for CL and MCL. Since treatment is often prolonged and potentially toxic, species determination may be desirable as some drugs are only effective against certain *Leishmania* species and only in the geographic region of the infection [87, 90].

Antimonial chemotherapy remains the most commonly used therapeutic option for New World CL because this disease tends to be more long-lasting and severe, and poses a higher risk of mucous involvement than its Old World counterpart [80]. Amphotericin B deoxycholate and pentamidine have been used as second-line drugs. Over the past 10 years, lipid formulations of amphotericin B and miltefosine have been approved for the treatment of all clinical forms of leishmaniasis. However, the efficacy and required dosage of several of these agents have not been established in all endemic areas and may even differ from area to area [90].

Pentavalent antimonials include meglumine antimoniate (Glucantime®; 81 mg Sb^{v+}/ml) and sodium stibogluconate (Pentostam®; 100 mg Sb^{v+}/ml). The recommended dose for New World CL is 10–20 mg Sb^{v+}/kg/day of Glucantime for a period of 20 days, with an efficacy of 53.6% [91] to 56.9% [99] for *L. guyanensis*, compared with 78% for *L. braziliensis* [92]. The recommended dose for MCL treatment is 20 mg Sb^{v+}/kg/day for a period of 30 days. Side effects include arthralgia, myalgia, loss of appetite, nausea, vomiting, abdominal pain, pruritus, fever, weakness, headache, dizziness, insomnia, edema, hepatitis, acute renal failure, pancreatitis, electrocardiographic changes, and bigeminal, polymorphous, and polyfocal extrasystoles [90].

Amphotericin B deoxycholate is a polyene antibiotic whose recommended dose is 0.5–1.0 mg/kg by intravenous infusion in 5% dextrose for 4 h, daily or every other day, in 15–20 doses. Fever, nausea, vomiting, and phlebitis at the infusion site are common side effects; nephrotoxicity may also occur. Other uncommon toxic effects include anemia, leukopenia, hypokalemia, and myocarditis [90].

Several formulations, including liposomal amphotericin B, amphotericin B lipid complex, and amphotericin B colloidal dispersion have been used for the treatment of all clinical forms of leishmaniasis. Their efficacy is similar to that of the deoxycholate drug, but lipid formulations of amphotericin B are significantly less toxic [93].

Pentamidine is a synthetic derivative of amidine administered intramuscularly or intravenously. The recommended schedule is a 3-dose regimen of 4 mg/kg every 72 h, with an efficacy of 60.3% for New World CL due to *L. guyanensis* [84]. A recent phase II pilot study showed that a single dose of 7 mg/kg might be as effective and safe as the three-dose regimen for the treatment of CL in the same geographic area [94]. Adverse effects are sterile abscesses at the injection site, nausea, vomiting, dizziness, adynamia, myalgia, headache, hypotension, syncope, transient hyperglycemia, and hypoglycemia.

Miltefosine is a phospholipid drug originally developed as an antineoplastic agent. It is the first clinically active oral antileishmanial drug commercially available for the treatment of CL [95]. The drug is registered for treatment of leishmaniasis in several countries and has been recently approved by the US Food and Drug Administration for the treatment of CL and MCL (due to *L. braziliensis*, *L. panamensis*, and *L. guyanensis*) [87]. Miltefosine is administered orally for 28 days at the daily dosage of 2.5 mg/kg for children aged 2–11 years; for patients aged ≥12 years, 50 mg/day for those weighing <25 kg, 100 mg/day for 25–50 kg body weight, and 150 mg/day for >50 kg body weight. The drug is contraindicated in pregnant women, and nursing mothers should be advised not to breastfeed during the treatment course and for 5 months thereafter. Common

reported gastrointestinal side effects are anorexia, nausea, vomiting, and diarrhea, which are usually brief and tend to resolve as treatment is continued [90]. The effectiveness of miltefosine has been variable in different *Leishmania* species causing CL. In CL caused by *L. guyanensis* its clinical efficacy was 71.4% [91], from 33% [57] to 75% [58] for *L. braziliensis*, 60% for *L. Mexicana* [57], 91% for *L. panamensis* [96], and 81.3% *L. major* [97]. Therefore, physicians should be aware that identification of *Leishmania* species may be necessary to better treat patients or tourists, especially those living in or traveling to Central and South America.

Ketoconazole, itraconazole, fluconazole, and allopurinol, all with discordant results, are reported as oral treatment options. Local therapeutic approaches include intralesional pentavalent antimonials [60, 61], topical application of paromycin sulfate [98, 99] and physical modalities such as cryotherapy, thermotherapy, curettage, and electrodissection [80].

In HIV-CL coinfected patients, the therapeutic options are mainly pentavalent antimony and amphotericin B in the same regimen used for immunocompetent patients. Pentamidine is not recommended as it may cause sterile abscess. Coinfected patients require close monitoring of CD4 cell count, and secondary prophylaxis with pentavalent antimony should be considered.

Prevention

To date, no vaccine or drugs to prevent *Leishmania* infection are available. Preventive measures are aimed at reducing the contact with sandflies. Travelers should be advised to avoid outdoor activities whenever possible, wear protective clothing, apply insect repellent, and sleep in air-conditioned or well-screened areas [100]. Measures to combat the vectors should be also employed.

Glossary

Amastigote Two developmental stages are formed (*Leishmania*): the amastigotes are small spherical nonflagellated cells ranging from 2 to 4 μm in diameter. The nucleus and kinetoplast are surrounded by small ring of vacuolated cytoplasm and the cells are among the smallest nucleated cells known.

Anergic pole/hyperergic pole The two pathogenicity extremes of the spectrum generally recognized are represented at the hypersensitivity pole by mucocutaneous leishmaniasis (MCL) and at the hyposensitivity pole by anergic diffuse cutaneous leishmaniasis (ADCL).

Colonization The human body harbors a large number of bacteria but their localization in healthy individuals is normally restricted to certain body areas such as the skin, the mucosae of buccal and nasal cavities, vagina, and, most importantly, the gastrointestinal tract. Colonization is the act of setting up a colony away from one's place of origin.

Ectoparasite A parasite that lives on or in the skin but not within the body.

Fomite A fomes or fomite is any nonliving object or substance capable of carrying infectious organisms, such as germs or parasites and hence transferring them from one individual to another. Skin cells, hair, clothing, and bedding are common hospital sources of contamination.

Hyaluronidase A family of enzymes that degrade hyaluronic acid.

Infestations Parasites, including harmful nanites, cause infestations, which are a type of affliction similar to diseases. Also known as or related to infestation by pediculus, pubic louse infestation, pediculosis pubis, and pediculosis.

Monilethrix A condition that affects hair growth. Its most characteristic feature is that individual strands of hair have a beaded appearance like the beads of a necklace.

Promastigote Two developmental stages are formed (*Leishmania*): amastigotes and promastigotes. Promastigotes are thin elongated cells with an anterior kinetoplast and an emergent free flagellum.

Proteases Any enzyme that performs proteolysis, that is, begins protein catabolism by hydrolysis of the peptide bonds that link amino acids together in a polypeptide chain.

Skin microbiota The skin flora, more properly referred to as the skin microbiota, are the microorganisms which reside on the skin.

Th1 response The Th1 response is characterized by the production of interferon-γ, which activates the bactericidal activities of macrophages, induces B cells to make opsonizing (coating) and complement-fixing antibodies, and leads to cell-mediated immunity.

Th2 response The Th2 response is characterized by the release of interleukin-5, which induces eosinophils in the clearance of parasites. Th2 also produce interleukin-4, which facilitates B-cell isotype switching. In general, Th2 responses are more effective against extracellular bacteria, parasites including helminths, and toxins.

Trichorrhexis nodosa A defect in the hair shaft characterized by thickening or weak points (nodes) that cause the hair to break off easily.

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Part III

Dermatologic Diseases in Public Health: Neoplasias

Precursor Lesions of Skin Cancer

13

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Key Points
- Review the relevant skin lesions that are skin cancer precursors
- Facilitate the clinical recognition of skin cancer precursor lesions
- Summarize the current treatment modalities and conduct of each skin cancer precursor lesion
- This chapter is divided into three main groups of precursor lesions: cutaneous melanoma, basocellular carcinoma, and spinocellular carcinoma.
- In the cutaneous melanoma precursors lesions group we discuss congenital melanocytic nevus, dysplastic nevus, and acquired melanocytic nevus.

- In the basocellular carcinoma precursor lesions group we discuss nevus sebaceus.
- In the spinocellular carcinoma precursor lesions group we discuss actinic keratoses, porokeratosis, cutaneous horn, chronic scars, oral leukoplakia and erythroplakia, oral lichen planus, lichen sclerosus, and precursor lesions of skin cancer related to human papillomavirus.

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Introduction

Skin cancer, more common than any other type of cancer [1], can be divided into two main groups: cutaneous melanoma (CM) and nonmelanoma skin cancer (NMSC), which includes basocellular carcinoma (BCC) and spinocellular carcinoma (SCC).

CM is the sixth most common neoplasia in men and the fifth most common in women. It comprises 5% of diagnosed skin cancers but is responsible for most of the deaths in this group [2]. According to the International Agency for Research on Cancer, 232,100 new cases of

melanoma were estimated worldwide in 2012, considering both sexes [3].

On the other hand the figures for NMSC are very difficult to estimate, as it is not mandatory to record these cases [4, 5]. The most recent study estimated 3.5 million new cases in 2.2 million people in the United States in 2006 [6]. Moreover, very significant costs are associated with skin cancer treatment, and it is among the five neoplasias that are most expensive to treat in the United States [7].

Although NMSCs usually grow slowly and do not often metastasize, especially BCC, these tumors may insidiously invade the local tissue, causing tissue destruction, functional impairment, and body disfigurement. BCC can also invade nerves and other vital structures, such as the eyes [8].

In view of the impact of skin cancer on public health, this chapter is dedicated to the recognition and treatment of melanoma and NMSC precursor lesions.

Cutaneous Melanoma Precursor Lesions

Approximately 65–80% of CMs begin in healthy skin (de novo melanoma) and thus 20–25% of these develop from a previous skin lesion that we can define as a precursor lesion [9–13].

Three main groups of pigmented cutaneous lesions can be CM precursors: congenital melanocytic nevus (CMN), dysplastic/atypical nevus, and acquired melanocytic nevus (AMN).

Congenital Melanocytic Nevus

CMN is a melanocytic nevus that is present at birth or, rarely, up to 2 years of age [14, 15]. Some researchers proposed a classification of CMN according to their larger diameter in adult life: small (<1.5 cm), intermediate (or medium) (1.5–19.9 cm), and large (or giant) (≥20 cm) [14, 16] (Fig. 13.1a, b).

CMN begins between the 5th and 24th week of pregnancy [17] and is believed to result from the rapid proliferation of melanocytic lineage cells resulting from some morphologic error of the neuroectoderm during the migration of the melanoblasts from the neural crest to the skin [14, 18, 19]. The earlier the acceleration process begins during embryogenesis, the larger and deeper the nevus will be [14].

The potential risk of developing melanoma from a CMN is probably related to its size; that is, the larger the nevus, the greater the risk. The risk of melanoma associated with a small CMN is considered low and probably no greater than that of an AMN [15].

On the other hand, controversy exists regarding intermediate CMN. A study followed 230 intermediate CMN in 227 patients over 6.7 years and did not detect the onset of melanoma during this period [20]. Another study evaluated the incidence of melanoma and mortality in 265 patients and did not detect melanoma in CMN of <5% of body area [21]. According to Alikhan et al. [22], most studies show a melanoma incidence <1% in small and medium-sized CMN, which is similar to the risk of CM over a lifetime (1.97%). Thus, recent studies suggest that the medium-sized (and small) CMN are not associated with a significant risk of CM [15].

On the other hand, the risk of CM associated with giant CMN (GCMN) is well established [14–16, 21, 22], and in up to 70% of cases it can occur before puberty [23]. Although the real incidence is still controversial, the estimated risk of patients with GCMN developing CM during their lifetime is 5–10% [14].

The incidence of GCMN is estimated as less than 1 in 20,000 newborns [6], and the prevalence varies from 0.5% to 31.7% [22].

Clinically, GCMN generally presents as a brownish lesion with defined margins and hypertrichosis [14]. However, its clinical presentation may vary individually and change with age. At birth they are usually lighter-colored, flat, and with little or no hairs, but over time their appear-
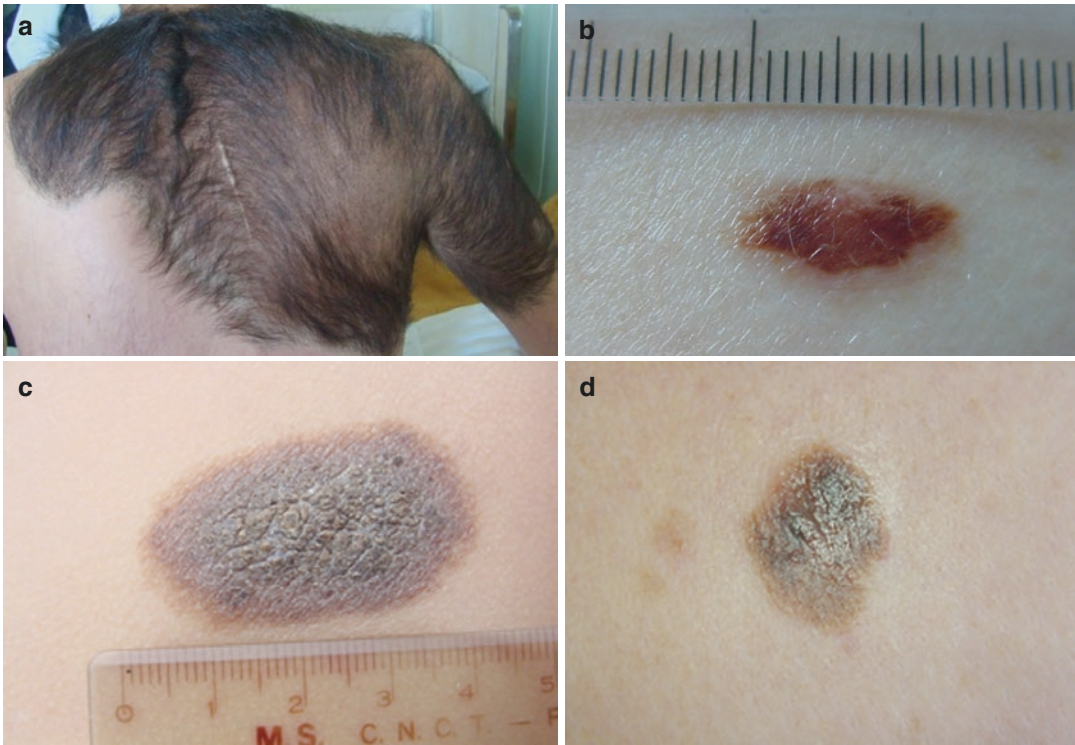
Fig. 13.1 Cutaneous melanoma precursor lesions. (**a**) Giant congenital melanocytic nevus on trunk with defined margins and hypertrichosis. (**b**) Dysplastic nevus with macular component and varied colors with size ≥5 mm. (**c**) Medium or intermediate congenital melanocytic nevus. (**d**) Acquired melanocytic nevus. (Photos b and c - Courtesy from Prof. Renan Bonamigo)

ance can change [14, 22]. A common change is the onset of macules or small papules, darkish brown and flat or slightly elevated in the initial lesion [22]. Most nevi become elevated, forming a plaque that may have a warty, papular, rough, or cerebriform surface [14, 22]. The most frequent site is the trunk, followed by the extremities and head, but it may affect more than one body segment [14]. It is common for benign melanocytic growth to occur, known as "proliferative nodules" in GCMN, which may be clinically and histologically confounded with CM. Moreover, GCMN are often associated with satellite CMN, smaller lesions that may be multiple [15, 22]. The presence of these satellite lesions may increase the risk for CM [23].

The diagnosis of GCMN is basically clinical [14]. Histologically, peculiar findings that may be present are nevic cells in the deep reticular dermis, which may reach the subcutaneous fat and fascia in addition to the adnexal structures, vascular walls, eccrine glands, collagen fibers, and cutaneous nerves [14, 15, 22]. The fact that nevic cells are deeper in the dermis is one of the reasons why dermatoscopy of little use in these cases. In addition, because of this particularity the CM related to GCMN are not of epidermal origin in up to two-thirds of cases, and generally occur in deeper layers of the dermis [24]. This leads to a later diagnosis of the neoplasia, since it is more difficult to detect through clinical tests [14], and contributes to a worse prognosis, because the presence of neoplastic cells in the deeper layers makes it easier for early metastasis to occur from tumor propagation via blood vessels and lymphatic vessels [25].

One of the serious complications of GCMN is neurocutaneous melanosis, a rare syndrome characterized by the presence of malignant or benign proliferations in the central nervous system (CNS), associated with melanocytic congenital lesions and clinical manifestations that are usually the consequence of increased intracranial pressure because the proliferations obstruct the ventricular system [14].

An interesting finding demonstrated by DeDavid et al. [26] was that only 50.7% of CM in individuals with GCMN involved the nevus. The remainder was primary tumor of the CNS, a metastatic tumor without a primary site, and CM unrelated to the nevus.

No single validated approach is used to manage GCMN [22]. The decision to remove a GCMN is individualized and based on the patient's age, site of the lesion, risk for CM, presence or absence of neurocutaneous melanosis, complexity of removal, cosmetic result, and the presence of modifications suggesting malignancy [14, 15]. Theoretically, prophylactic excision would provide the best chance of reducing malignant change in the GMN because it removes the tissue (and the nevic cells). However, no evidence indicates that removing the nevus is prophylactic for the occurrence of CM, and no study has documented the benefit of excision over clinical observation [14, 27].

It is important to carry out periodic follow-ups, besides palpating the lesion and lymph nodes and photographing the nevus to make monitoring easier. Even the patients who have had the nevus completely removed must be monitored periodically for easier early detection of malignancies [14].

Dysplastic Nevus

Dysplastic nevus (DN) is described as a continuum between the common acquired nevus and the melanoma, since it is morphologically and biologically the intermediate between these two entities [28]. Since it was reported for the first time by Clark in 1978, its definition, classification, and biological importance have been discussed, and so far there is no consensus about its nomenclature [28, 29].

Often the terms atypical nevus and dysplastic nevus have been used inadequately as synonyms, since the former is a clinical finding and the latter a histologic finding. Moreover, a few lesions without clinical atypia can reveal dysplasia, and the contrary may also occur [30]. However, as yet there is no single definition of nomenclature for these lesions accepted by all dermatologists and pathologists [28]. For didactic reasons, in this chapter we use the term dysplastic nevus.

The mean clinical prevalence of DN has been reported as between 2% and 18% of the Caucasian population with histologic findings of dysplasia in 10% [31].

DN is important primarily because it simulates CM, besides being a phenotypic marker of individuals at increased risk for CM [30–34]. The largest meta-analysis performed until now showed that, among 13 studies with dichotomic data, the presence of any DN (the article uses the term atypical nevus) increased the risk for melanoma tenfold compared with the absence of DN (relative risk (RR) = 10.12; 95% confidence interval (CI) 5.04–20.32). When 15 studies were evaluated with continuous data according to the number of dysplastic nevi, patients with a history of a single nevus showed RR = 1.60 (95% CI 1.38–1.85) for developing CM, rising to 10.49 (95% CI 5.05–21.76) for those with five DN [34].

DN syndrome, characterized by the presence of more than 100 common nevi including at least one dysplastic and one larger than 8 mm, carries an even greater risk for CM. This syndrome may be sporadic or familial, with different classifications based on the degree of relationship and the personal history of DN or melanoma [31].

The role of DN as a precursor is less important because there is little evidence that a DN will progress to a CM at a greater rate than a common nevus [30, 32]. A calculation based on the fre-

quency of DN and CM estimated that only 1 in 10,000 DN will progress to CM per year [35].

Clinically, the Agency for Research on Cancer proposed a protocol that includes the following characteristics: presence of a macular component in at least one area of the lesion plus the presence of one of the following: ill-defined border, size ≥5 mm, varied colors, irregular border, and erythema [36] (Fig. 13.1c). The DN typically becomes visible in puberty and predominates in people younger than 30–40 years, compared with older populations [31].

There is an extensive discussion regarding the histologic criteria of DN. The most important are the presence of cytologic atypia and architectural disorder [32]. According to the World Health Organization (WHO), two major criteria and at least two minor ones are needed for its diagnosis (Table 13.1). Using these criteria, there is 92% concordance in distinguishing between the common melanocytic nevi, DN and CM [37]. Some studies have also already shown a relation between the degree of dysplasia and the risk for CM, which was greater in moderate and severe dysplasias [38, 39].

According to the available evidence, the clinical diagnosis of DN (or DN syndrome) does not require histologic confirmation, since most of the DN will not progress to CM unless there is clinical suspicion of the latter [30–33, 35]. Therefore prophylactic removal is not cost effective, besides giving the patients a false feeling of safety, since the risk for melanoma may remain after the nevus is removed [35].

The general approach to the care of patients with DN includes obtaining a detailed history, including information on the history of skin cancer, previous removals of nevi, episodes of sunburn and exposure to ultraviolet (UV) radiation, and family history of melanoma and DN [31, 35]. This information will help stratify the risk for CM.

It is necessary to perform a complete examination of the skin including protected areas and the scalp. The revisions can be done 6 months after the initial baseline examination and then once a year, or more frequent follow-up if there is a personal history of melanoma. Patients should be advised to request an earlier visit if they notice a newly appearing lesion to be suspicious or a change in a pre-existing lesion [35]. At each visit it is important to reiterate preventive and educational measures regarding protection and precautions against sunlight [31, 35].

We can use diagnostic aids such as dermoscopy, total body photography, and digital imaging devices to facilitate the early detection of melanoma. Dermoscopy has been shown to significantly improve diagnostic accuracy, although the diagnostic performance depends on examiner experience [40]. Similarly, using photography has been shown to improve the diagnosis of subtly changing melanocytic lesions that do not meet clinical criteria for melanoma, facilitating early diagnosis as well as limiting unnecessary biopsies of clinically suspicious lesions that are stable over time [41].

When any suspicious lesions are detected, biopsy is necessary. The recommendation is an excision with 1- to 3-mm margins and also a deep margin of subcutaneous fat. However, if the suspicion for melanoma is low or excisional biopsy is unreasonable based on anatomic location, other techniques such as shaving or incisional biopsy may be appropriate [42, 43].

Acquired Melanocytic Nevus

It has already been demonstrated in several studies that AMN is a risk marker for CM, especially when a large number of them are apparent [44, 45].

Table 13.1 World Health Organization (WHO) histologic criteria for dysplastic nevus

Major criteria	Minor criteria
Basilar proliferation of atypical melanocytes that must extend at least 3 rete ridges beyond the dermal component	Lamellar fibrosis or concentric eosinophilic fibrosis
	Neovascularization
Organization of this proliferation in a lentiginous or epithelioid-cell pattern	Inflammatory response
	Fusion of rete ridges

A meta-analysis performed in 2005 observed a dose-response pattern with increased RR for the development of CM as the number of common nevi increased. When individuals with up to 15 nevi all over their body were considered as baseline, an RR of 1.47 (95% CI 1.36–1.59) was obtained for patients with 16–40 common nevi, 2.24 (1.90–2.64) for those with 41–60 common nevi, 3.26 (2.55–4.15) for those with 61–80 nevi, 4.74 (3.44–6.53) for those with 81–100 nevi, and 6.89 (4.63–10.25) for patients with 101–120 common nevi [34].

Melanomas associated with nevi occur more frequently on the trunk and in younger patients, and are more commonly of the superficial spreading type [46–49] (Fig. 13.1d).

However, their role as precursors is still controversial [50, 51]. The most convincing evidence in favor of this theory is the association between nevus and CM observed both clinically and histologically, since approximately 20–30% of the melanomas are associated with nevi in histology [46, 47, 50].

A study evaluated the frequency of the histologic association of benign melanocytic lesions with 289 cases of CM that were at most 1 mm thick, and detected that 41% of the cases were associated with AMN [50].

Moreover, information about the molecular profile of the associated CM and AMN can help clarify the pathogenesis of this subtype of melanoma [50]. In a recent study, the status of six genes was evaluated in 61 cases of melanomas and their associated nevi, whereby a concordance rate of 66.7% was found: 46.6% of the CM and 51.6% of the nevi showed mutations in BRAF V600E, and 17% of the melanomas and 12% of the nevi showed mutations in NRAS [52]. These data supported the hypothesis that nevus associated with melanoma is their precursor [50].

Given these data, when a nevus has changed over time or clinically leads to a suspicion of melanoma, it is indicated for removal [15].

Basocellular Carcinoma Precursor Lesions

Nevus Sebaceus

Nevus sebaceus (NS) is a hamartoma of epithelial and nonepithelial origin that is often referred to as an organoid nevus because it may contain any or all components of the skin [53, 54]. It usually presents as a round, oval, or linear, smooth, yellowish-orange plaque on the head, neck, and scalp (87–95% of cases) leading to alopecia [55] (Fig. 13.2). Histology reveals hyperkeratosis, acanthosis, increased sebaceous lobules, primitive hair follicles, and apocrine proliferation [56].

The natural history of NS may be divided into three stages. Early in life, the lesion is characterized by papillomatous hyperplasia and the presence of immature hair follicles. Then at puberty, when hormonal changes result in the development of the sebaceous glands and apocrine glands, the lesion is transformed from a smooth into a verrucous plaque. Finally in the third stage, various benign and malignant neoplasms may occur within the lesion [57].

In a revision that compiled a list of the reported malignant tumors developing within NS, the most common malignancy observed was BCC (119 reported), more than all of the other kinds of malignant tumors together [57]. It is interesting

Fig. 13.2 Nevus sebaceus on the scalp of a child

that in this review it was observed that the earlier studies report more malignant growths compared with more recent studies. It is likely that the incidence of BCC has been overestimated, as basaloid proliferation is a common finding, and some pathologists may label this condition as BCC rather than benign trichoblastoma [58].

Otherwise, in a retrospective study of 596 surgical excision specimens of NS, more than 90% of the associated tumors were benign. The three most common tumors were syringocystadenoma papilliferum, trichoblastoma, and trichilemmoma. There were only five cases of true BCC (0.8%) and no other malignant tumors [59].

A more recent retrospective analysis reviewed 707 cases and malignant tumors were present in 2.5% of the specimens, almost exclusively in adults. BCC represented 1.1%, followed by spinocellular carcinoma (0.57%) [60].

The definitive treatment of NS is full-thickness dermal and epidermal excision, although there is an ongoing debate regarding whether NS should be excised and, if so, when. Excision may be justified for cosmetic reasons or to avoid the formation of tumors [57].

According to the finding that trichoblastomas predominate within NS, not BCC, close observation of the lesion may be a better approach than prophylactic excision. Nevertheless, authors who report the development of invasive malignant tumors in NS still recommend prophylactic excision [57].

The unknown risk of malignant transformation, lesion expansion, increased lesion friability, associated bleeding or itching, and the aesthetic concerns associated with scalp alopecia might influence the decision for early excision. However, the risks of general anesthesia in children and the risks of excision, such as bleeding, infection, and scarring, also need to be considered [61].

Ultimately, the decision of whether to excise prophylactically should be determined after a thorough review of the options as well as personal and medical evaluation of the patient [57].

Spinocellular Carcinoma Precursor Lesions

Actinic Keratosis

Actinic keratoses (AK) are epidermal lesions at the initial clinical stage of a biological continuum that may culminate in SCC [62]. They generally result from prolonged exposure to nonionizing radiation, especially UV radiation from the sun [2]. AK has been characterized historically as a premalignant or precursor lesion of skin cancer, because it presents atypical keratinocytes confined in the epidermis [63].

More than 1 million new cases are reported annually and it thus represents approximately 14% of the visits to the dermatologist [64]. Besides its epidemiologic impact, AK is also a marker of photodamage representing the main risk factor for SCC [62]. The probability that an AK will develop into an SCC was estimated as 0.075–0.096% per lesion per year [65]. Thus, for a person with an average of 7.7 AK lesions on their skin, the incidence of SCC would be 10.2% in 10 years [66]. Hurwitz and Monger reported that 97% of SCC are associated with previous AK [67]. Although the rate of regression of single AK lesions was generally seen to be 20–30% with up to 63% in one study, spontaneous regression of complete fields of AK was only seen in 0–7.2% of patients [68].

Risk factors for the development of AK include old age, male gender, cumulative sun exposure, and fair skin type. Immunosuppression and genetic syndromes associated with impaired DNA repair mechanisms, deficiency in melanin biosynthesis, or an increased vulnerability to UV radiation damage also result in a higher risk for the development of AK [69].

The classical primary lesion is characterized by a rough erythematous papule covered with white to yellow scale that can vary from millimeters to confluent plaques several centimeters in diameter [63] (Fig. 13.3). The lesions are typically concentrated in areas with greater
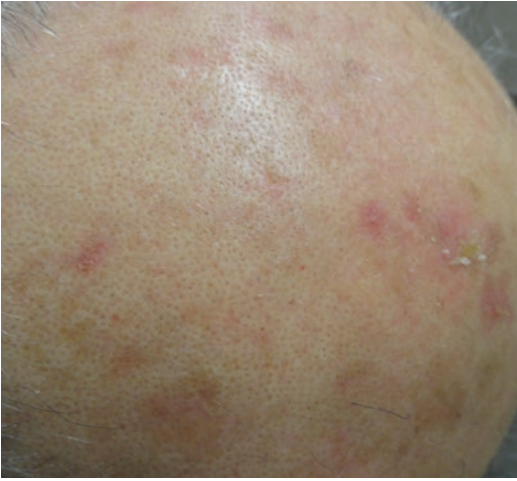
Fig. 13.3 Actinic keratosis. Multiple rough erythematous plaques covered with scale

exposure to sunlight, and 80% are on the head, neck, and upper limbs [62]. There are other variations in the clinical presentation, and they can present as hyperkeratotic, pigmented, lichenoid, and atrophic AK, and as actinic cheilitis [63]. Most of the lesions are asymptomatic, but some may cause pruritus or a burning sensation [70].

The essential alterations in histopathology are atypical keratinocytes, hyperkeratosis, parakeratosis, especially covering the atypical keratinocytes, perivascular or lichenoid lymphocytes, and solar elastosis in the dermis [71].

The available data indicate that the presence of AK without adequate treatment is a dynamic but chronic condition, with a low chance of sustained spontaneous complete regression. This, associated with the risk of progression to invasive SCC, makes the treatment of the AK lesions necessary [68].

Protection from sunlight is an important part of management of patients with AK. There are three components to photoprotection: behavioral modification by seeking shade during the peak ultraviolet B (UVB) hours of 10 am–2 pm, wearing photoprotective outfit (including clothing, wide-brimmed hat, and sunglasses), and application of broad-spectrum sunscreens with a sun protection factor 30 or higher [69].

Currently there are several types of therapy available, the optimum choice depending on the

number of lesions and regions involved, whether the lesions can be distinguished from each other or not, and whether there are contiguous areas with chronic actinic damage and hyperkeratosis.

According to the guideline published in 2015, for up to five visible or palpable lesions per field or region of the body affected, the best recommendations are cryotherapy followed by curetting, 5-fluorouracil (5-FU) 5% or 0.5%, imiquimod 3.75 or 5%, ingenol mebutate 0.015/0.05%, and photodynamic therapy [69].

Otherwise, for multiple lesions (six or more) and contiguous areas with actinic damage and hyperkeratosis, the strongest recommendations are for 5-FU 0.5%, imiquimod 3.75%, ingenol mebutate 0.015/0.05%, or photodynamic therapy followed by cryotherapy, diclofenac sodium 3%, 5-FU 5%, imiquimod 5%, and CO_2 laser or Er:YAG-laser [69].

Porokeratosis

Porokeratosis (PK) is a group of cutaneous entities characterized by disordering of epidermal keratinization, presence of a cornoid lamella, and a predisposition to develop malignant transformation [72].

The most commonly reported malignant lesions are carcinoma in situ, SCC and, more rarely, BCC [73]. There are five major clinical variants of PK that are differentiated purely on clinical criteria [74, 75], and malignant degeneration has been found in all forms with a reported incidence of 6.9–11.6% [73].

Disseminated superficial actinic porokeratosis (DSAP) is the most common type, representing 42% of cases [76]. DSAP consists of multiple annular, hyperkeratotic, brownish macules measuring 2–5 mm in diameter with a bilateral distribution on sun-exposed areas, particularly the extremities. The center of the lesion is minimally atrophic or depressed and the border spreads centrifugally in raised ridges [77] (Fig. 13.4a). DSAP can affect people of all ages, but it affects more women in their third to fourth decade of life [77].
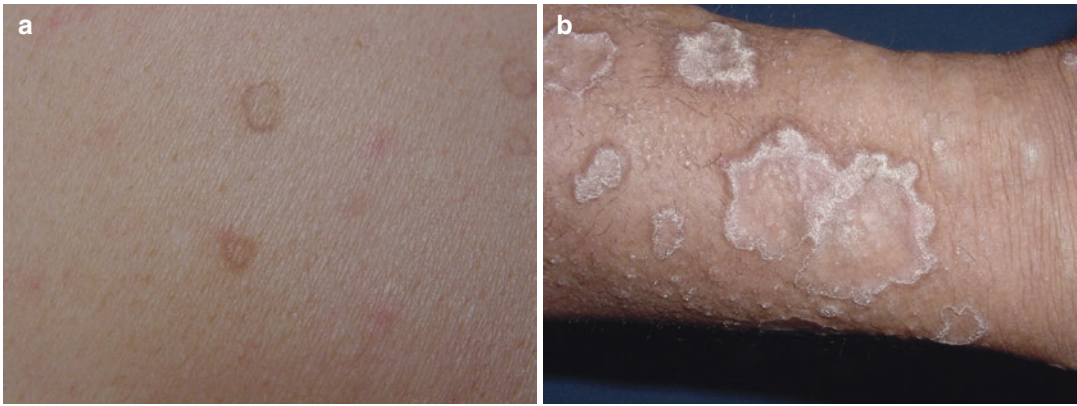
Fig. 13.4 Porokeratosis. (**a**) Disseminated superficial actinic porokeratosis with typical peripheral keratotic rims. (**b**) Porokeratosis of Mibelli, a large plaque with keratotic borders

Other variants are the classic plaque form of Mibelli (PM) and linear porokeratosis (LP), accounting, respectively, for 35.5% and 13% of cases [76]. PM begins in childhood as an asymptomatic, small, brown to skin-colored keratotic papule that gradually enlarges and over time can form a plaque that may measure several centimeters in diameter [78] (Fig. 13.4b).

Other less common types are porokeratosis palmaris and plantaris disseminata (PPPD) and punctate porokeratosis [75, 79]. Simultaneous presentation of several types of PK can occur but is rarely reported [75].

The diagnosis of all types of PK is typically based on clinical examination and the typical histologic feature is the cornoid lamella, a narrow column of tightly packed parakeratotic cells that correspond to the clinically observed raised hyperkeratotic border [78].

Although the pathogenesis is unknown, immunosuppression and actinic exposure predispose to their development [72].

Malignant transformation has been reported to occur in 7.6% of PM, 3.4% of DSAP, 19% of LP, and 9.5% of PPPD cases [79] and the average latency period is 36 years [72].

The precise mechanism by which malignant degeneration develops in PK is not yet completely understood. A genetic mechanism of allelic losses at an early stage of embryonic development has been suggested [80]. However, no molecular data have been presented to support this hypothesis [72].

Malignant lesions seem to be more frequent in nonexposed skin, in large PK lesions, in patients with a history of ionizing radiation exposure, in the linear type, and in multiple patterns of PK [72, 81].

PK does not usually need treatment, but in some cases may be necessary because of its potential for malignant progression and for cosmetic purposes [77]. No controlled studies are available in the literature. Although several therapeutic options have been reported, none of them has shown consistent and long-lasting efficacy [82].

The local destructive modalities include surgical excision, especially when few lesions are present, curettage, dermabrasion, cryotherapy (freezing cycle of 30 s), laser ablation (including erbium, CO_2, or Q-switched ruby), and photodynamic therapy [82–84].

Among the topical agents, 5-FU 0.5–5% applied once or twice daily for 3 weeks to several months has proved effective in some cases of PM, DSAP, and LP. Imiquimod 5% cream once daily 3–7 days/week for 4–24 weeks, also has been reported with a good response [81, 85]. Other options such as local retinoids, keratolytic agents, steroids, and emollients have been used in PK with variable results [82].

Systemic treatment with oral retinoids has been described with conflicting results. These agents have been given at doses varying from 20 to 75 mg/day over 1–5 months [82, 84].

Patients at risk, for instance with long-standing and large lesions, should be followed to detect any malignancies, which should be given specific treatment [81, 82].

Fig. 13.5 A cutaneous horn with a keratotic plaque. (Courtesy of Dermatology Service of UFCSPA)

Cutaneous Horn

Cutaneous horn (CH) is a clinical term for a firm, white to yellow, conical, keratotic papule or plaque ranging from a few millimeters to several centimeters in size [78]. CH resembles animal horns at first glance and is mainly composed of compact keratin [86] (Fig. 13.5).

Most of the lesions develop on the face and scalp (about 30%), but any part of the body can be involved, usually sun-exposed areas [86, 87].

Although the precise pathogenesis of horn formation is not fully understood, abnormal accumulation, excessive adhesiveness, and compaction of keratin have been suggested [88].

CH can be derived from a variety of epidermal lesions. According to Yu et al., the primary lesions associated with CH may be benign, premalignant, or malignant in 61%, 23.2%, and 15.7% of cases, respectively. These conditions include seborrheic keratosis, viral warts, molluscum contagiosum, trichilemmoma, hemangioma, sebaceous adenoma, BCC, actinic keratosis, Bowen's disease, keratoacanthoma, Kaposi's sarcoma, SCC, and sebaceous carcinoma [89]. Schosser et al. evaluated 230 lesions of CH, of which the most common horn base entity was actinic keratoses in 37.4% of cases [90].

SCC is the most common neoplasia associated with malignant-based horn [86]. A retrospective histopathologic study of 222 cases of CH found that SCC was present in 93.75% of the malignant cases evaluated [91].

Risk factors for underlying malignancy include advanced age, male sex, wide base or a low height-to-base ratio (large or giant horns), presence on a sun-exposed location, and history of actinic keratosis or skin cancer [87, 88]. Surrounding inflammation and an infiltrated base may indicate malignancy [87].

Findings from a study that correlated clinical and dermoscopic features of CH with histopathology showed that, when presenting as a horn, SCC tends to have height less than the base diameter, less terrace morphology, a higher incidence of base erythema, and more pain [92].

Histopathology shows a compact, diffuse hyperkeratosis with parakeratosis, and the findings at the lesion base will vary according to the underlying process [87].

The treatment for cutaneous horns is excision achieving a good specimen from the base for histopathologic evaluation, to rule out underlying malignancy and guide potential further therapy [78, 87].

Chronic and Burn Scars

Malignant degeneration of chronic ulcers and burn scars has been described extensively in the literature. The first description dates from the first century AD by Celsus, and the term 'Marjolin's ulcer' to describe malignant change of chronic ulcer was created in 1903 by Da Costa [93, 94]. Today this term refers to carcinomas arising both from chronically inflamed and scarred skin [95] (see Fig. 13.6).

The incidence is of 0.1–2.5% and the main etiology tends to be postburn scars and traumatic wounds [96].

In a review of 412 cases of neoplasms from burn scars, 71% of the cases were SCC, followed by BCC (12%) and melanoma (6%) [93]. The average latency period from injury to onset of malignancy is 31 years and the average age at onset is in the fifth decade of life [93, 94]. Poor prognosis compared with conventional skin cancer is another characteristic, attributable to the
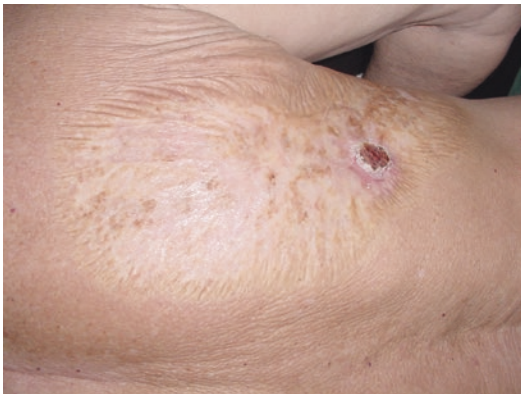
Fig. 13.6 Spinocellular carcinoma arising from a burn scar

high rate of recurrence (16%), lymph node metastasis (22%), distant metastasis (14%), and mortality (21%) [93]. Moreover, their aggressive nature contributes to the poor prognosis since SCC arising from scars are ten times more likely to metastasize than those arising from actinic damage [95].

Anatomically there is a preponderance of carcinomas on the extremities in contrast to spontaneously occurring SCC, which usually appears on the head and neck [97]. Burn scar cancer is typically seen on the lower extremities (43.7%), upper extremities (22.4%), trunk (11.5%), and head (22.4%), respectively [94], and occurs mostly in burns that have not been grafted [97].

The pathogenesis is not completely known. Repetitive trauma, long-standing epidermal hyperplasia, and increased mitotic activity at the edges of these chronic wounds may predispose to malignant transformation [94, 97]. Another possibility is that the reduced vascular tissue and lymphatic channels in scars may make it easier for the tumor to resist the body's usual defenses [97].

At the molecular level, some studies discussed the abnormalities in the p53 gene in patients with burn scar carcinoma [98]. Besides this, Lee et al. showed that burn scar SCC cases have Fas gene mutations in the apoptosis function region [99].

Factors such as high histologic grade, tumor location (especially on the lower extremities), large tumor diameter (>10 cm), and regional lymphadenopathy on presentation are poor prognostic factors. Acute type, location on the head, neck, or upper limbs, exophytic form, well differentiated grade, peritumoral T-lymphocyte infiltration, and absent metastasis on presentation have a better prognosis [94, 97].

If the neoplasia is confirmed, surgery is the treatment of choice. Wide surgical excision with margins of 2–4 cm is generally recommended [95, 96]. Lymph node dissection is advised in the presence of clinically palpable nodes, but not as a prophylactic measure. Moreover, Marjolin's ulcers have a poor response to radiotherapy and chemotherapy, probably because of poor vascularity caused by extensive fibrosis [95].

Excision and grafting of deep burns and unstable scars, as well as close follow-up of nonhealing ulcerated burn scars, is essential for the prevention and early detection of neoplasia [93].

Oral Leukoplakia and Erythroplakia

Oral leukoplakia (OL) is currently defined by the WHO as "a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no risk" [100] and erythroplakia as "a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease" [100, 101]. Both are classified as oral potentially malignant disorders (OPMDs) [100].

OL is the most common OPMD [102]. According to a systematic review, the global prevalence is estimated as 2.6% (95% CI 1.72–2.74%) [103]. The frequency of epithelial dysplasia, carcinoma in situ, or invasive oral spinocellular carcinoma (OSCC) in leukoplakias varies from 8.6% to 60.0% [102]. The global malignant transformation rate is estimated as 1.36% per year (95% CI 0.69–2.03%) [103].

Erythroplakia is rarer, with a prevalence that varies between 0.02% and 0.83% [103]. Nevertheless, the risk of malignant progression is the highest among OPMD, which approaches 55–65% in some studies [102].

OL are usually found in middle-aged and elderly persons in developed nations, mostly occurring between the fourth and seventh decades

of life, while in the developing world they may occur some 5–10 years earlier. Males are predominantly affected, but most studies record the development of OSCC more frequently in females [105].

The vast majority of lesions are associated with tobacco use (previous or current), although around 10% of lesions appear to have no known cause. The regression/disappearance of many lesions following abstinence supports the importance of tobacco in the etiology of leukoplakia [105]. Areca nut use is also an etiologic factor [100]. The roles of alcohol and human papillomavirus (HPV) infection in the etiology of OL are unclear at present [105].

There are two main clinical variants of OL: homogeneous leukoplakia, presenting as a uniformly white, flat, or slightly wrinkled plaque, containing many fine cracks or fissures and with a low risk of malignant transformation, and non-homogeneous leukoplakia, with a higher risk of malignancy (four- to sevenfold) [100, 105].

The latter can present a warty or nodular appearance, perhaps predominantly white with red areas or largely red with white speckles (erythroleukoplakia). Those containing nodular or red areas have been shown to have a greater risk of malignant transformation than the uniformly white ones [105].

Another form of OL is proliferative verrucous leukoplakia (PVL), which presents with multiple, simultaneous leukoplakias, as the disease is visibly multifocal and frequently covers a wide area [100]. It has a high risk of becoming dysplastic and turning into SCC [104].

Factors apparently associated with an increased likelihood of development of OSCC are anatomic site (tongue, floor of mouth, and retromolar/soft palate complex appear to be twice as likely to develop OSCC as those on the buccal mucosa, palate, or gingiva), non-homogeneous type, larger lesions covering several intraoral subsites, duration of the lesion, and age of patients (older patients, particularly females, are more at risk than younger patients). Those who have never used tobacco are paradoxically at greater risk than smokers [105].

On the other hand, erythroplakia is clinically characterized by a flat or even depressed erythematous change of the mucosa, usually solitary and asymptomatic, most commonly affecting the soft palate, floor of the mouth, and buccal mucosa [104, 106]. As OL, it occurs mainly in middle-aged and elderly men, and alcohol consumption and tobacco are possible etiologic factors [104, 106, 107].

Both OL and erythroplakia must be biopsied. The definitive diagnosis is made when any etiologic cause has been excluded and histopathology has not confirmed any other specific disorder [100]. The next step is to evaluate the presence of dysplasia, as it is the strongest predictor of future malignant transformation. Thus, lesions with the highest grade of dysplasia are thought to have the greatest probability of malignant transformation [100, 101]. Dysplasia is observed in nearly all cases of erythroplakia and 1–30% of oral leukoplakia cases at the time of diagnosis [101]. Erythroplakia also presents as carcinoma in situ or invasive carcinoma at the time of biopsy, and for this reason should be excised with a clear margin [100, 106].

There is no consensus regarding the management of leukoplakia, with some favoring an observational attitude toward dysplasia while others favor excision. Among the arguments against removal are the high rate of recurrence and that some dysplasia (especially mild dysplasia) regresses [102]. Besides this, surgical intervention reduces the risk but does not completely eliminate it [101]. Nevertheless, usually moderate or severe dysplastic lesions are removed, but there is no scientific basis from a prospective, randomized controlled trial for this conduct.

Local excision is desirable if the lesion is small and when it would cause minimal morbidity to the patient. When the lesion is large and a resection would compromise the patient functionally, laser ablation (usually CO_2) is recommended [108].

The follow-up intervals are not evidence based but based on clinicians' subjective assessment [100]. Rhodus et al. recommend frequent follow-up examination (<6 months) depending on the diagnosis and clinical scenario, with rebiopsy of any suspicious areas if indicated [109].

An educational as well as a personalized approach is recommended with counseling to stop smoking and consuming alcohol [110].

Oral Lichen Planus

Lichen planus is a mucocutaneous disease characterized by an unspecific chronic inflammatory process, culminating in intense destruction of the basal layer of the epithelium [111]. Here we discuss a specific type of lichen planus, oral lichen planus (OLP).

The prevalence of OLP reported in the literature is between 0.5% and 2.2% with a mean age of 55 years. It affects women more than men, and rarely children and adolescents [112].

The first case of SCC arising in OLP was described by Hallapeau in 1910, since when numerous retrospective studies and case reports have been published [112].

However, it is a subject with controversial results in the literature, owing to the great variability of its incidence across populations, criticism regarding the inclusion criteria used in most studies, lack of adequate data in the initial diagnosis of OLP, lack of information such as historical exposure to carcinogens, and the development of carcinomas at anatomic sites remote from the OLP in some of these studies [112, 113].

Nevertheless, the WHO classifies OLP as a potentially malignant disorder, the range of malignant transformation varying between 0.04% and 1.74% per year [112, 113].

A review of 11,225 OLP cases found that a malignant transformation occurred in 183 (1.63%) approximately 6 years after the initial diagnosis, with a mean rate of 0.27% per year [113]. By comparison, the estimated incidence of oral cancer in Brazil according to the National Cancer Institute (INCA) in 2016 for males is approximately 0.008% [114].

OLP presents as white striations/papules/ plaques, erythema, erosions, or blisters affecting predominantly the buccal mucosa, tongue, and gingiva. Lesions are typically bilateral and often appear as a mixture of clinical subtypes. The most common clinical presentation is a reticular form with interlacing white keratotic lines (known as Wickham's striae) with an erythematous border (see Fig. 13.7). Symptoms such as sensitivity and pain may occur [115, 116].

Fig. 13.7 Oral lichen planus. White striations on the oral mucosa

Malignant transformation is more likely to occur in atrophic, erosive, or ulcerative lesions [112, 113, 115]. The last two predispose the mucosa to damage from carcinogenic agents such as tobacco and alcohol. However, other unknown extrinsic factors may be involved as some patients do not have a history of exposure [112].

It is possible that *Candida albicans* has a role in the development of malignancy because it is able to produce carcinogenic substances such as acetaldehyde [112, 117]. Another factor that may be involved is immunomodulating agents used in the treatment of LP. They have a potent anti-inflammatory effect that could promote the progression of LP to malignancy by way of reduced symptoms [112]. Furthermore, the presence of chronic inflammation and the continuous epithelial wound healing may increase the likelihood of cancer-forming gene mutations [115].

Biopsy is important to exclude malignancy and to differentiate OLP from other diseases. The histology is characterized by a dense subepithelial band of chronic inflammatory cells, usually T lymphocytes, which can transgress the basement membrane and reach the epithelium. Another feature is the degeneration of basal keratinocytes, forming the colloid bodies (eosinophilic globules) [112, 115].

Investigating the use of any systemic drug is also important in a patient with a suspicion of OLP, as oral mucosal lichenoid lesions may simulate OLP [115].

Treatment aims to control the symptoms and monitor dysplastic changes [112, 116]. Topical corticosteroids are the mainstay in controlling mild to moderately symptomatic lesions. Options include 0.05% clobetasol propionate gel, 0.1% or 0.05% betamethasone valerate gel, 0.05% fluocinonide gel, 0.05% clobetasol butyrate ointment or cream, and 0.1% triamcinolone acetonide ointment. These agents can be used up to three times a day since a thin layer is applied [116, 118]

Other topical options include tacrolimus or pimecrolimus in solution or cream, retinoic acid, and cyclosporine [112].

In patients with a widespread symptomatic lesion, options such as 1.0 mg/ml aqueous triamcinolone acetonide or 0.1 mg/ml dexamethasone elixir are possible. It is recommended to gargle with 5 ml of the solution for 2 min after meals. For recalcitrant or extensive lesions, subcutaneous injection of 0.2–0.4 ml of a 10 mg/ml solution of triamcinolone acetonide is another option [116].

For recalcitrant lesions that fail to respond to topical therapy, systemic corticosteroids can be tried, but with low evidence (there are no controlled studies evaluating this treatment).

Prednisone in a dose of 0.50–0.75 mg/kg per day can cause a significant response within 1–2 weeks. For longer periods the steroid dosage must be gradually tapered off [112, 116]

Other treatment modalities include retinoids and vitamin A analogs, psoralen combined with UV-A (PUVA), griseofulvin, levamisole, dapsone, and thalidomide. However, the evidence of the efficacy of these treatment approaches is not established [112, 116].

Because of the possible risk of SCC in patients with OLP, long-term follow-up is essential. Biannual evaluation is recommended and lesions should be rebiopsied as indicated [112, 115]. Also important is the advice to eliminate smoking and alcohol consumption [115].

Lichen Sclerosus

Lichen sclerosus (LS), also known as lichen sclerosus et atrophicus or balanitis xerotica obliterans, is an autoimmune, inflammatory dermatosis, characterized by a lymphocytic response that has a predilection for the genital skin in both sexes and an association with several other autoimmune diseases [119].

Its precise prevalence and incidence is unknown. Women are more affected than men, and both females and males have two peak ages of presentation: in the prepubertal and postmenopausal years, and in young boys and adult men, respectively [119, 120].

The etiology is unknown, although autoimmune, genetic, hormonal, and infectious factors have been implicated in its pathogenesis [121, 122].

The genital skin is mainly affected, although extragenital involvement is also possible [121, 123]. The typical lesions are porcelain-white papules and plaques but telangiectasias, fissures, ulcerations, and erosions can occur (Fig. 13.8). When symptoms are present, itching is the most common. Pain and dyspareunia may be a consequence of erosions, fissures, and introital narrowing. Phimosis can be a result of LS in men, leading to erectile dysfunction and painful erections [119, 121].

Fig. 13.8 Lichen sclerosus. White and atrophic plaque on genital skin

The presence of epidermal atrophy, superficial dermal edema associated with an underlying chronic inflammatory infiltrate, classically described as a "band-like" pattern, is characteristic at histology. Vacuolization of the basal layer, flattening of rete ridges, loss of elastic fibers, and homogenized dermal collagen can also be present [124, 125].

The association between SCC has been described principally with female genital LS and less commonly in penile LS. Extragenital lesions appear to carry no risk of malignancy [119, 120].

Despite the low related risk of between 1% and 7% [119, 120, 126], studies indicate that LS is present in up to 61% of histopathologic examinations of vulvar SCC [127].

In vulvar SCC two pathogenic pathways are involved: HPV-dependent and HPV-independent. The HPV-dependent pathway accounts for 20–40% of cases, is more common in younger women, and usually has vulvar intraepithelial neoplasia as a precursor lesion [128].

The non-HPV pathway is associated with LS and occurs in older women [119, 128]. In this case, the precursor lesion is the differentiated vulvar intraepithelial neoplasia, with a higher malignant potential and worse prognosis compared with SCC associated with HPV [128]. It appears that the chronic inflammation of the LS may cause molecular alterations that facilitate neoplastic proliferation [121].

In men, although less common, the association between SCC and LS has also been described. Barbagli et al. reviewed clinically and histologically 130 cases of male genital LS and found 11 cases (8.4%) with premalignant or malignant histopathologic features including 7 (64%) with SCC [129]. Another retrospective study evaluated 18 cases of histologically proven penile SCC and found histologic features of LS in 8 (44%) [130].

HPV also seems to exert a role in the pathogenesis of SCC, although this issue is controversial. Nasca et al. evaluated the presence of HPV by polymerase chain reaction (PCR) in 46 penile LS cases and compared them with a control group. They detected the presence of HPV in eight cases (17.4%) and in four controls (8.7%),

with an odds ratio of 2.55 and 95% CI of 0.73–8.89 [131].

Biopsy is indicated for patients with persistent ulcers, erosions, hyperkeratosis, and fixed erythematous areas to exclude intraepithelial neoplasia or invasive SCC [119].

According to the latest guideline to date, very potent or potent topical corticosteroids are the first line of therapy for LS. Long-term use appears safe and effective if needed, especially in active disease. Clobetasol propionate 0.05% cream or preferably ointment is the most studied. Although the frequency of application and maintenance treatment is under discussion, a common practice is to use it once or twice daily for 3 months, with a possible reduction in frequency after 1 month, and then as necessary [122].

Intralesional corticosteroids such as triamcinolone acetonide injections or a solution containing 2 mg of dexamethasone had a positive effect on pruritus and physical signs such as disease progression and scarring in vulval and penile LS, and may be an option in patients unable to use topical corticosteroids or with a resistant itch [122].

Topical calcineurin inhibitors (tacrolimus and pimecrolimus) seem to be an effective alternative to strong topical steroids in the treatment of genital LS, especially in children [119, 122]. Another recommendation is to use emollients to relieve the symptoms.

If standard therapy for LS is unsuccessful, other options include PUVA, photodynamic therapy, oral retinoids, systemic glucocorticosteroids, oral cyclosporine, methotrexate, hydroxycarbamide, cycloferon, ceftriaxone, penicillin G, sulfasalazine, and vitamin A combined with vitamin E or vitamin D. However, most of these have a very low level of evidence and grade of recommendation [119, 122].

Surgery is reserved for penile LS with symptoms due to persistent phimosis or meatal stenosis, and in women is only indicated for premalignant change or an invasive SCC and for highly selected symptomatic LS with complications of scarring [119, 122].

Long-term follow-up is appropriate for patients with genital LS associated with symptoms, localized skin thickening, previous cancer, or vulval intraepithelial neoplasia [119].

Precursor Lesions of Skin Cancer Related to Human Papillomavirus

The HPVs consist of a heterogeneous group of nonenveloped, double-stranded DNA viruses that display a distinct tropism for mucosal or cutaneous squamous epithelia [132, 133].

To date nearly 200 types of HPV have been discovered, of which approximately 50 infect the genital area and are related to a variety of skin manifestations ranging from common warts to malignancies [134].

The risk for persistence and progression to cancer precursor lesions varies according to HPV type, host factors, and the presence of cofactors such as smoking, immunosuppression, high parity, and hormonal contraceptive use [135], but the strongest risk factor for the development of malignancies associated with HPV is persistent oncogenic HPV infection (defined as HPV positivity at two or more visits) [136, 137]. Infection by specific high-risk types of HPV, particularly 16 and 18, is strongly associated with cancer. Together they account for about 70% of cervical cancers worldwide [136, 138]. Moreover, other cancers such as anal, penile, vulvar, vaginal, and oropharyngeal have been associated with high-risk HPV [132, 136]

HPV 16 is the most common type with a prevalence ranging from 3% to 4% in North America, followed by HPV 18. The prevalence shows a peak in women up to 25 years of age with a subsequent decline until age of 35–44 years. The infection is transmitted through direct skin-to-skin or skin-to-mucosa contact, and the number of sexual partners has been shown to be the main determinant of anogenital HPV infection both in women and men [136].

The virus specifically infects the stratified epithelium, and systemic dissemination does not occur [134]. Most HPV infections are self-limited and are asymptomatic or unrecognized, and take years or decades to undergo malignant transformation [134, 137].

Most of the clinically apparent anogenital warts are caused by low-risk HPV types 6 or 11 and are rarely associated with high-risk type HPV (Fig. 13.9). When it happens it is usually a

Fig. 13.9 Multiple genital warts. Both exophytic and sessile lesions are present. (Courtesy of Dermatology Service of UFCSPA)

coinfection with HPV 6 or 11, and foci of high-grade squamous intraepithelial lesions, particularly in persons who have HIV infection, may occur in these cases [137].

Outstanding among the lesions caused by low-risk HPV types but with a possible malignant transformation is the Buschke–Löwenstein tumor or giant condylomata accuminata. This is a large destructive tumor on the genitalia associated with HPV types 6 or 11 and despite its histologic benign presentation, focal malignant transformation into squamous cell carcinoma can occur.

Other rare skin manifestations of oncogenic strains (16 and 18) are Bowenoid papulosis and erythroplasia of Queyrat, no longer considered precursor lesions but SCC in situ. They are, therefore, discussed in another chapter.

Subclinical lesions are also possible, which are visible only with the use of enhancing techniques, such as colposcopy, when the application of 3–5% acetic acid for 5–10 min might turn the affected areas white [134].

Anogenital warts are usually diagnosed by inspection and can be confirmed by biopsy in specific cases: atypical lesions (pigmented, indurated, affixed to underlying tissue, bleeding, or ulcerated), lesions that do not respond to standard therapy, when the disease worsens during therapy, and if the diagnosis is uncertain [137].

Table 13.2 Patient-applied treatment options for anogenital warts caused by HPV

Treatment modality	Posology	Adverse effects
Imiquimod 5% cream	Once at bedtime, 3 times per week for up to 16 weeks. Wash the area with soap and water 6–10 h after the application	Local inflammatory reactions such as redness, irritation, induration, ulceration/erosions, vesicles, and hypopigmentation
Imiquimod 3.75% cream	Once at bedtime for up 8 weeks. Wash the area with soap and water 6–10 h after the application	
Podophyllotoxin 0.5% solution or gel or Podophyllotoxin 0.15% cream	Twice daily for 3 days, followed by 4 rest days	Mild to moderate pain and local irritation
	Can be repeated for up to four cycles	
	Do not exceed 10 cm² of treated area	
Sinecatechins 15% or 10% ointment	Three times daily for 12–16 weeks. Do not wash after use	Erythema, pruritus/burning, pain, ulceration, edema, induration, vesicular rash

Currently there are two HPV vaccines that can prevent diseases and cancers caused by HPV (but not treat existing HPV or genital warts): the bivalent vaccine (Cervarix), which prevents infection with HPV types 16 and 18, and the quadrivalent vaccine (Gardasil), which prevents infection with HPV types 6, 11, 16, and 18. These vaccines are recommended routinely for boys and girls aged 9–13 years in a scheme of a 3-dose series of intramuscular injections over a 6-month period, with the second and third doses given 1–2 and 6 months after the first dose, respectively [135, 137]

The treatment options for anogenital warts include destructive methods that may reduce but probably do not eradicate HPV, thus leading to possible recurrence after treatment, especially in the first 3 months [137].

Therapy can be performed at home or in the clinic. Among the home options are imiquimod, podophyllotoxin, and sinecatechins (a green-tea extract with an active product called catechins) (see Table 13.2). Among the options for therapy in the clinic are cryotherapy, surgical removal (by tangential excision, curettage, laser, or electrosurgery), and trichloroacetic acid 80–90% solution applied once per week for a maximum of 8–10 weeks [137, 139].

The choice of treatment depends on wart size and number, and anatomic site, patient preference, cost, convenience, adverse effects, and provider experience [137]. Follow-up is recommended every 4 weeks, switching treatments if the response is inadequate [139].

Using condoms and limiting the number of sexual partners can decrease the chances of infection but do not fully protect against HPV [137].

Glossary

Actinic keratoses Epidermal lesions at the initial clinical stage of a biological continuum that may culminate in spinocellular carcinoma. They generally result from prolonged exposure to nonionizing radiation, especially ultraviolet. It has been characterized as a premalignant or precursor lesion of skin cancer, because it presents atypical keratinocytes confined in the epidermis.

Congenital melanocytic nevus Melanocytic nevus that is present at birth or rarely up to 2 years of age. It is believed to result from the rapid proliferation of melanocytic lineage cells due to some morphologic error of the neuroectoderm, during the migration of the melanoblasts from the neural crest to the skin.

Cutaneous horn A clinical term for a firm, white to yellow, conical, keratotic papule or plaque ranging from a few millimeters to several centimeters in size. Spinocellular carcinoma is the most common neoplasia associated with malignant-based horn.

Dysplastic nevus Described as a continuum between the common acquired nevus and the melanoma, since it is morphologically and biologically the intermediate between these two entities.

Erythroplakia A fiery red patch that cannot be characterized clinically or pathologically as any other definable disease. It is classified as an oral potentially malignant disorder.

Giant congenital melanocytic nevus Congenital melanocytic nevus of ≥20 cm that generally presents as a brownish lesion with defined margins and hypertrichosis. The association with melanoma is well established.

Human papillomaviruses Consist of a heterogeneous group of nonenveloped, double-stranded DNA viruses that display a distinct tropism for mucosal or cutaneous squamous epithelia. They are associated with development of malignancies, particularly high-risk HPV types.

Lichen sclerosus An autoimmune, inflammatory dermatosis, characterized by a lymphocytic response that has a predilection for the genital skin in both sexes, and an association with several other autoimmune diseases.

Marjolin's ulcer This term refers to carcinomas arising both from chronically inflamed and scarred skin.

Nevus sebaceus A hamartoma of epithelial and nonepithelial origin that is often referred to as an organoid nevus because it may contain any or all components of the skin.

Oral leukoplakia A white plaque of questionable risk having excluded (other) known diseases or disorders that carry no risk. It is classified as an oral potentially malignant disorder.

Porokeratosis A group of cutaneous entities characterized by disordering of epidermal keratinization, presence of a cornoid lamella, and a predisposition to develop malignant transformation.

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Basal Cell Carcinoma

14

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Key Points

- Basal cell carcinoma (BCC) of the skin is the most frequent cancer in the Caucasian population
- BCC has been related to increased ultraviolet (UV) exposure
- Mutated *PTCH1* gene is associated with BCC in patients with Gorlin's syndrome as well with sporadic BCC
- BCC's classical clinical presentation is a slow-growing pearly papule, showing telangiectatic vessels
- Dermoscopy is an important technique, enhancing sensibility and specificity in the diagnosis of BCC

- The anatomopathologic examination is central to the diagnosis and classification of BCC
- The gold-standard approach and the most often used for BCC is surgical treatment
- High-risk tumors should be approached preferably with Mohs micrographic surgery

Epidemiology

Basal cell carcinoma (BCC) of the skin is the most frequent cancer among the Caucasian population, and its incidence is still growing [1]. Precise epidemiologic data could be underestimated as a result of undernotification, great variability exists between different geographic regions.

BCC is responsible for 25% of all types of cancer, being the most frequent of the skin cancers, representing 70% of all nonmelanoma skin cancers, with a ratio of 4:1 in relation to squamous cell carcinoma (SCC) [2]. In Brazil 80,850 new cases in males and 94,910 in females were estimated in 2016 [3].

The incidence of BCC is increasing. A North American study showed a 15% incidence

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elevation in the 15 years from 1998 to 2012 [4]. The increased longevity of the population and concomitant elevated incidence of BCC in the older population, especially those older than 40 years, may explain the recent increased incidence [5].

Pathogenesis

The origin of BCC cells is still a matter of controversy. For a long time it was supposed to originate from pluripotent cells of the bulge in the hair follicles; recently it has been related to pluripotent cells from interfollicular epidermal cells and the hair follicle infundibulum [6].

Although the etiologic evidence of actinic damage in SCC is more obvious, BCC has also been related to increased ultraviolet exposure, either in sporadic or continuous form, with outdoor workers showing a higher incidence of BCC [7].

Genetic factors are also important in the pathogenesis of BCC. The evidence for the association of a mutated *PTCH1* gene with BCC in patients with Gorlin's syndrome as well as the association of other mutations in this biological pathway with sporadic BCC supports its etiologic importance [7].

Clinical Presentation

BCC is described classically as a slow-growing pearly papule, showing telangiectatic vessels that can progress to nodules and ulceration. The clinical presentation may vary according to different histologic subtypes. It occurs predominantly on the face, especially on the nose, not always showing preference for sun-exposed areas [8].

BCC can be classified clinically as nodular, superficial, morphoeic, and fibroepithelioma of Pinkus. The presence of melanin is related to the presence of brown or bluish coloration seen in the pigmented variant, and the clinical types are described here [9].

Nodular BCC

Nodular is the most frequent clinical type of BCC. In early stages it is represented clinically by a pearly papule with variable degrees of telangiectasia, distinctive clinical findings of this tumor (Fig. 14.1). The lesion progresses slowly to a nodule, sometimes ulcerating (Fig. 14.2). The presence of melanic pigment characterizes the pigmented variant BCC (Fig. 14.3). Neglected lesions can grow significantly, resulting in extensive necrosis and ulceration, defined clinically as *ulcus rodens* (rodent ulcer), in analogy to a rat bite.

Superficial BCC

Superficial BCC is characterized clinically as a red scaly patch, sometimes showing a discrete pearly, elevated border. This clinical type is frequently located on sun-exposed areas (Fig. 14.4).

Fig. 14.1 Pearly papule with telangiectasia in a nodular BCC on the left nasal ala

Fig. 14.2 Nodular ulcerated BCC on the nasal tip

Fig. 14.3 Pigmented BCC on the nasal ala

Fig. 14.5 Ill-defined plaque on the forehead and eyebrow region of a morphoeic basal cell carcinoma
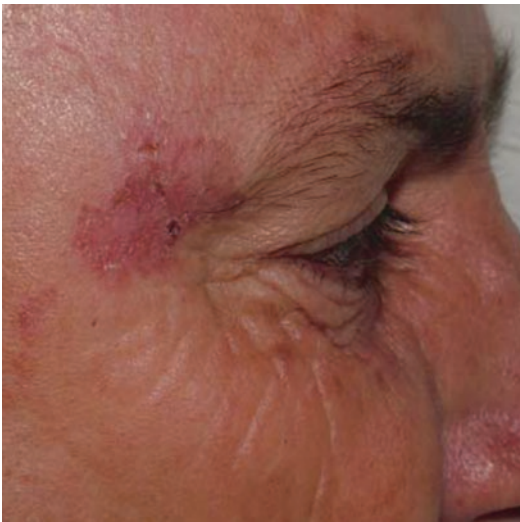
Fig. 14.4 Red scaly patch on a sun-exposed area in a superficial BCC on the temporal region

Table 14.1 Diagnostic criteria for basal cell carcinoma

1. *Clinical presentation:*
Pearly papule with telangiectasias that can progress to nodules and ulceration
Morphoeic BCC usually presents as an ill-defined plaque
Superficial BCC presents as a red scaly plaque
Pigment can be present in all variants, being defined as pigmented BCC
Dermoscopic findings: short fine telangiectasias, leaf areas, and blue-gray ovoid nests
2. *Pathology:*
Confirmation of diagnosis by biopsy and definition of histologic risk factors
3. *Radiologic findings:*
To investigate invasion to deeper anatomic structures or to investigate local dissemination

Morphoeic BCC

The morphoeic variant is represented clinically as an atrophic plaque, similar to morphoea, showing a scar-like surface with ill-defined margins and a firm consistency on palpation (Fig. 14.5). In this variant ulceration tends to be a late event.

Pinkus Fibroepithelioma

Fibroepithelioma of Pinkus is a rare variant of BCC frequently located on the lower back, and characterized clinically as a slightly erythematous pedunculated papule or nodule with a rubbery consistency.

Diagnosis

The diagnosis of BCC is essentially clinical (Table 14.1). As suggested by the clinical findings described, it occurs predominantly on individuals with a clear complexion. Dermoscopy is an important technique, enhancing sensibility and specificity in the diagnosis of BCC, either pigmented or not [10]. The most validated findings are short fine telangiectasias, leaf areas, and blue-gray ovoid nests [11].

Complementary Examinations

Biopsy and pathology are essential for the diagnosis and subtype definition, with a direct impact on treatment decision [12]. Imaging methods are used to enhance diagnostic specificity and sensibility, as well as for defining clinical margins; the methods used are confocal microscopy, optical coherence tomography, and radiologic examinations that can be used for staging.

Histopathology

Histopathology is the gold-standard complementary examination for the diagnosis and staging of BCC. Nests of basaloid cells with peripheral palisade and clefts between the stroma and tumor cells are typical findings. BCC can be classified histologically by its growth pattern or histologic differentiation. Expansive growth is related to a less aggressive form of BCC (Fig. 14.6); the chordonal or infiltrative variants have more subclinical extension, behaving as high-risk lesions (Fig. 14.7) [13].

Classification according to histologic subtype can be subdivided into nodular, superficial, infiltrative, morphoeic, micronodular, and mixed type, the latter being a combination of two or more subtypes [14]. The nodular variant is the less aggressive subtype. Superficial BCC sometimes shows ill-defined borders enhancing the risk of recurrence, while infiltrative and morphoeic subtypes are aggressive [14].

Metatypical BCC, also known as basosquamous cell carcinoma, is a more aggressive form of BCC that shows areas of squamous differentiation, with a variable degree of keratinization [13].

Perineural and/or angiolymphatic invasion are important findings that correlate with a more aggressive behavior and subclinical extension [15].

Imaging Methods

The use of medical imaging methods are indicated for advanced cases when deep structural invasion is suspected clinically. In such situations computed tomography and magnetic resonance imaging are the most commonly used methods.
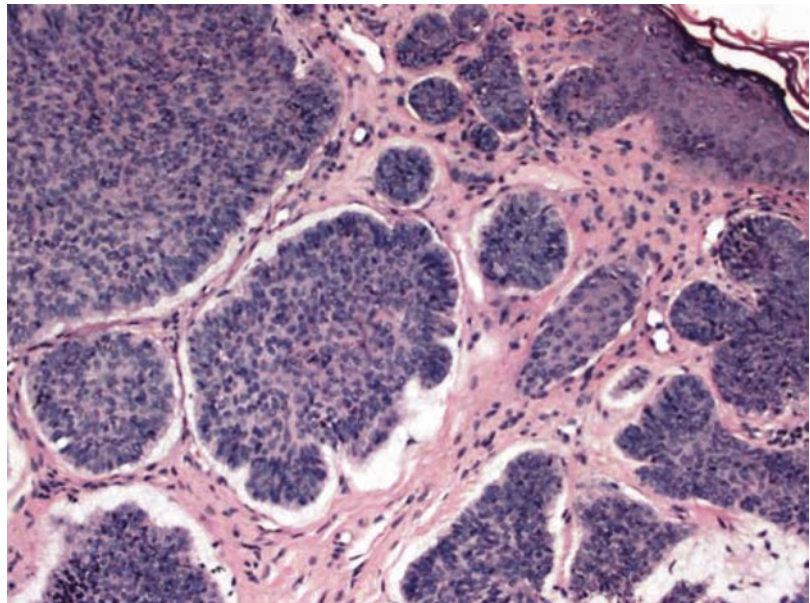
Fig. 14.6 Histopathology of basal cell carcinoma showing expansive growth pattern (hematoxylin–eosin) (Courtesy of Lismary Mesquita, MD)

Fig. 14.7 Histopathology of basal cell carcinoma showing infiltrative growth pattern (hematoxylin–eosin) (Courtesy of Lismary Mesquita, MD)
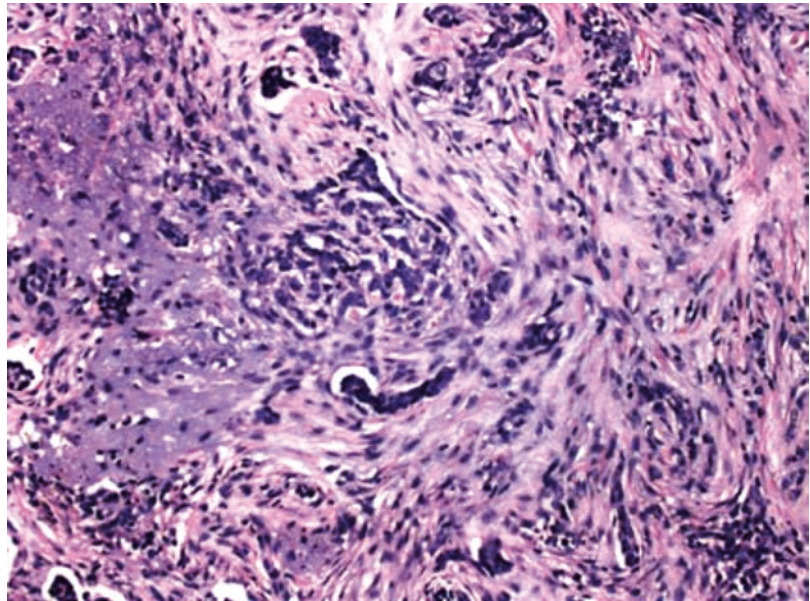
Table 14.2 Differential diagnosis of BCC according to clinical subtype and nature of the lesion

		Nature of lesion	
		Benign	Malignant
Clinical subtype	Superficial	Eczema, psoriasis	SCC in situ
	Nodular	Sebaceous hyperplasia, intradermal melanocytic nevus tricoepithelioma, molluscum contagiosum	SCC, Merkel cell tumor, amelanotic melanoma
	Morphoeic	Scar, dermatofibroma	Adnexal microcystic carcinoma, DFSP
	Pigmented	Melanocytic nevus, seborrheic keratosis	Melanoma
	Fibroepithelial	Fibroepithelioma	

SCC squamous cell carcinoma, *DFSP* dermatofibrosarcoma protuberans

High-frequency ultrasonography (15–22 MHz) is also indicated to evaluate deep invasion [16].

Other imaging methods such as confocal microscopy and optical coherence tomography have been used to enhance diagnostic accuracy and definition of surgical margins, although their use is limited because of high cost and low availability.

Differential Diagnosis

Differential diagnosis of BCC must be divided by its clinical subtypes and will include benign and malignant lesions (Table 14.2). Papular lesions

must be differentiated from nodular BCC, erythematous scaly plaque from superficial BCC, and atrophic and depressed lesions from morphoeic BCC [17].

Therapeutic Approach

A great variety of techniques are available for the treatment of BCC. Prior to choosing the treatment method a biopsy must be performed to confirm the diagnosis and define the histologic subtype, which will define the biological behavior of the lesion (Table 14.3). Nonsurgical

Table 14.3 Classification criteria for BCC biological behavior

		BCC risk factors				
		Anatomic location	Diameter	Histologic subtype	Primary/recurrent	Perineural invasion
Biological behavior	Nonaggressive	Low risk	<20 mm	Nodular	Primary lesion	No
		Moderate risk	<10 mm			
	Aggressive	Low risk	>20 mm	Morphoeic, micronodular, metatypical, or infiltrative	Recurrent lesion	Yes
		Moderate risk	>10 mm			
		High risk	Any size			

High-risk areas: facial "H" region, pre- and postauricular, temporal, eyelids, nose, lips, chin, mandible, genitalia, hands, and feet
Moderate-risk areas: cheeks, forehead, neck, scalp, and pretibia
Low-risk areas: trunk and limbs (excluding hands and feet) (Fig. 14.9)
Note: superficial BCC can be ill defined, presenting a higher risk of recurrence

Table 14.4 Treatment modality recommended according to the biological behavior of the BCC

Biological behavior	Non-aggressive	Aggressive
Treatment modality	Surgical excision (4-mm margins)	Surgical excision (at least 6-mm margins)
	Curettage and electrodesiccation[a]	Mohs micrographic surgery
	Cryosurgery[a]	

Note: superficial BCC can be treated by nonsurgical methods such as photodynamic therapy or imiquimod, when located in low-risk areas
[a]Curettage and electrodesiccation and cryosurgery are only suited for primary BCC, smaller than 1 cm in low-risk areas

methods such as methyl aminolevulinate photodynamic therapy (MAL/PDT), cryosurgery, curettage, and electrodesiccation are blind methods without control of histologic margin. Surgical excision with conventional pathologic margin control are indicated for low-risk lesions, whereas higher-risk lesions must be submitted to extensive surgical margins or preferentially to Mohs micrographic surgery because of the higher rate of recurrence (Table 14.4) [12].

Nonsurgical Treatment Methods

Nonsurgical treatments such as MAL/PDT and imiquimod are indicated for superficial BCC with recurrence rates of 27.2% and 16.6%, respectively, in a 1-year follow up study [18]. A randomized 5-year follow-up study showed a recurrence rate of 22% in the treatment of superficial BCC with MAL/PDT [19]. These modalities are indicated for the treatment of superficial BCC without other risk factors and if located in a low-risk anatomic region.

Curettage and Electrodesiccation

This technique is based on the principle of a defective cellular adhesion between BCC cells and the surrounding stroma, which would facilitate the shedding of tumoral cells. The curettage must be performed in a vigorous way, in different directions, followed by eletrocauterization of the wound, a procedure that should be repeated for three times. It is contraindicated in high-risk BCC, especially in lesions with a fibrous stroma, such as the morphoeic subtype, whereby tumor removal is highly unexpected [7].

Cryosurgery

This treatment modality is based on the principle of selected cryonecrosis, whereby a cryogene, such as liquid nitrogen, induces necrosis of tumoral tissue by freezing it to −50° to −60 °C, preserving the surrounding tissue. A double freeze cycle is recommended for the treatment of BCC, but this technique is only indicated for non-aggressive lesions in a low-risk area [7].

Surgical Excision

Surgical excision consists in surgical removal of the lesion with safe surgical margins of surrounding normal tissue, which may vary according to the aggressiveness of the lesion; the resulting specimen is then submitted for conventional histopathologic analysis. The safety margins recommended for a 95% chance of completely removing the lesion are 4 mm for low-risk lesions and those smaller than 2 cm, while for larger lesions with other risk factors margins of at least 6 mm are recommended. The rate of complete removal of high-risk lesions with 5-mm margins is 82%, while margins of 11–13 mm will remove 95% of the lesions [20], indicating that the subclinical invasion of the lesion can be extensive.

In conventional surgical excisions, the histologic margins are sampled by the bread-loaf section or cross-section techniques; these methods will examine less than 1% of surgical margins, which could result in a false-negative margin in the pathologic analysis.

Mohs Micrographic Surgery

Micrographic surgery is a term used to describe techniques of surgical removal of skin cancer, the use of a graphic reference map, and complete histologic control of surgical margins. Acknowledging the work of Doctor Frederic Mohs, his name is used to define this important technique for skin cancer removal.

The technique involves the surgical removal of the tumor in a specialized way in order to obtain a specimen that will be oriented and submitted to frozen sections, sampling the totality of its margins and maintaining a rigorous orientation control (Fig. 14.8).
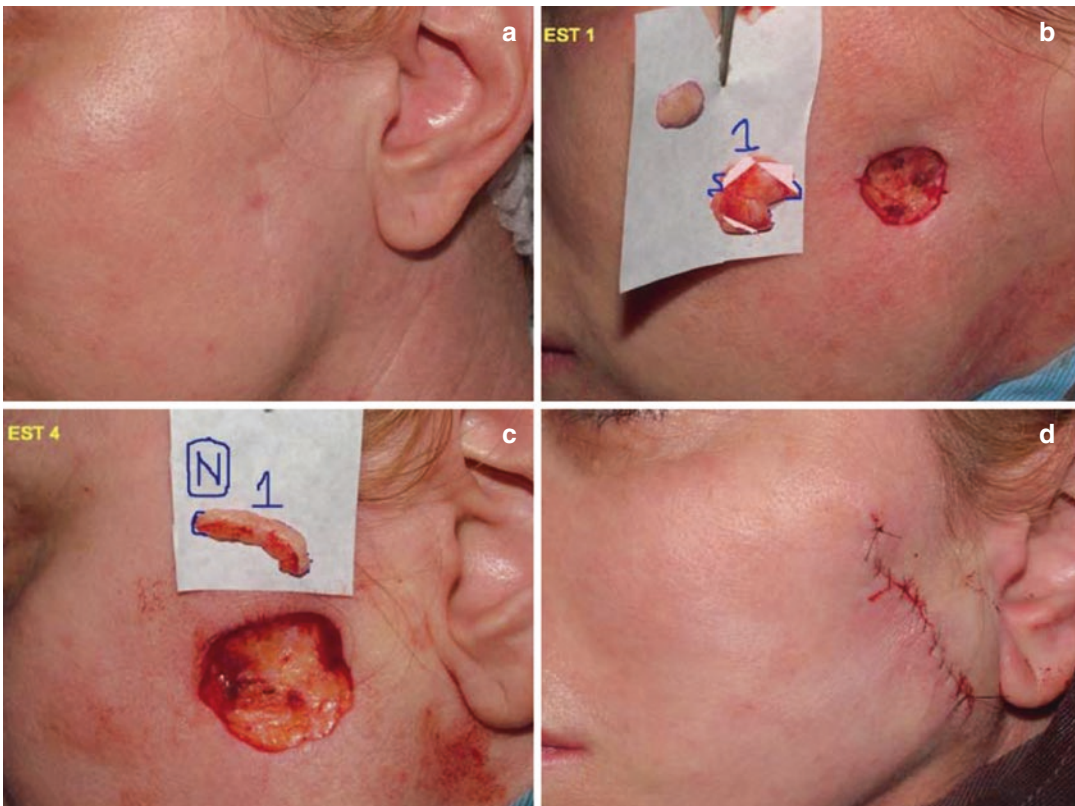
Fig. 14.8 Recurrent superficial BCC treated by Mohs micrographic surgery. (**a**) Recurrent superficial BCC. (**b**) Digital map of the first stage of the lesion removal. (**c**) Free margins after the fourth stage of Mohs surgery. (**d**) Simple suture repair
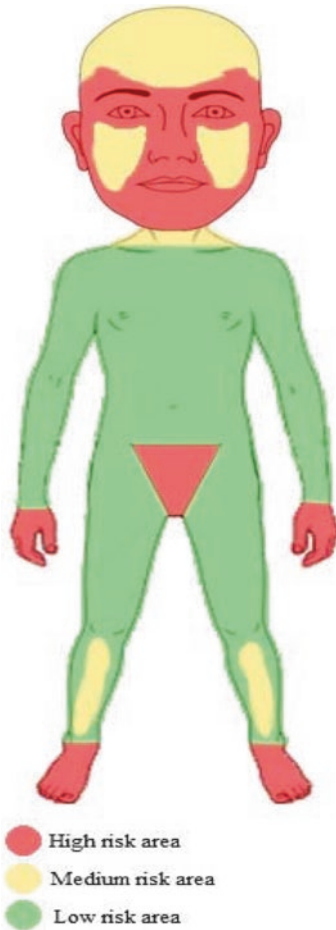
Fig. 14.9 Risk areas

The Mohs technique is indicated for aggressive lesions, lesions in areas of higher recurrence risk, and areas where tissue sparing is vital for functional and cosmetic preservation. A 5-year follow-up study showed a 99% cure rate for primary BCCs and 94.4% for recurrent lesions [12].

Follow-up

All individuals submitted to treatment of BCC should be followed for at least 5 years because of the recurrence risk, and be submitted to a complete body inspection because of the risk of a second primary lesion.

Glossary

Confocal microscopy Noninvasive imaging technique that enables in vivo visualization of the skin structure in real time.

Dermoscopy Noninvasive diagnostic technique for the in vivo observation of skin lesions with a dermatoscope, allowing magnification of the lesion.

Gorlin's syndrome Also known as nevoid basal cell carcinoma syndrome, it is characterized by developmental anomalies, such as odontogenic keratocysts of the mandible, bifid ribs, palmoplantar pits and tumors, and especially multiple BCCs.

Mohs micrographic surgery A microscopically controlled surgery used to treat different types of skin cancer, developed in 1938 by Frederic Mohs.

Optical coherence tomography Noninvasive imaging examination that uses light waves to take cross-sectional pictures of the skin structure.

Photodynamic therapy Treatment that uses a photosensitizer or photosensitizing agent that will be absorbed by the target cell, and a particular type of light that will react with the photosensitizer and cause cellular death.

PTCH1, **patched 1 gene** This gene encodes the protein receptor for the sonic hedgehog, a molecule implicated in the formation of embryonic structures and in tumorigenesis. Mutations of this gene have been associated with basal cell nevus syndrome and sporadic BCC.

Telangiectasias Dilated capillaries that appear clinically as red linear vessels with spidery appearance on the surface of the skin.

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Squamous Cell Carcinoma

15

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Key Points
- SCC incidence has increased over the last decades
- UV radiation induces mutations of the *TP53* tumor supressor gene
- HPV is more present in SCCs than in patients' nonlesional skin
- Actinic keratosis, traditionally regarded as a premalignant condition, is nowadays classified by many as an intraepithelial form of SCC
- SCC occurring in an area previously affected by trauma or burn scarring is called Marjolin's ulcer
- The anatomopathologic examination is central to the diagnosis and classification of SCC

- The gold-standard and most often used approach for SCC is surgical treatment
- High-risk tumors should be dealt with preferably by using Mohs micrographic surgery

Epidemiology

Squamous cell carcinoma (SCC) of the skin is a malignant neoplasia presenting a classical multistage behavior involving carcinogenesis, precursor lesions, tumoral progression, and potential for the development of metastatic disease [1]. SCC is the second most common type of skin cancer after basal cell carcinoma (BCC); these two neoplasias belong to a group known as nonmelanoma skin cancer (NMSC).

In Brazil, NMSC is the most frequent neoplasia in both sexes, corresponding to 25% of all malignant tumors registered; BCCs represent 70% and SCCs 25% of all NMSCs. It is noteworthy that the lack of compulsory notification may underestimate its incidence. In Brazil 175,760 new cases were expected in 2016, 80,850 in males and 94,910 in females [2]. In the United States in 2012, 5.4 million cases of NMSC among 3.3 million people were diagnosed [3, 4].

SCC is frequently located in the head and neck and limbs, especially in photoexposed areas

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[5]. It is three times more frequent in men than in women, and its incidence increases with age. Individuals with a light complexion are affected more frequently; SCC is rare in blacks and Asian ethnic groups; nevertheless, it is still the most commonly found skin cancer in those populations [6, 7], in whom SCC often occurs in nonexposed skin regions [8].

The increased incidence of SCC over the past decades may be explained by earlier detection, increased outdoor activities, artificial tanning, frequent use of immunosuppressive drugs, and increased average life expectancy [4, 9]. Despite the higher incidence of SCC, a decrease in mortality has been observed, possibly attributable to early detection and effective treatment in the early stages of the disease [10, 11]. Approximately 30–50% of SCC carriers may develop another primary SCC in 5 years [12, 13].

The exact incidence of SCC mortality is unknown, although a retrospective cohort study with a median of 50 months of follow-up showed a 3.7% incidence of metastasis and a 2.1% disease-specific death risk [14].

Etiopathogenesis

Extrinsic and intrinsic factors may be involved in the etiopathogenesis of SCC; the main factors are described above.

Ultraviolet Radiation Exposure

Ultraviolet radiation (UVR) is the most important environmental risk factor for SCC and is involved in all stages of carcinogenesis, initiation, promotion, and progression, being defined as a complete carcinogen. UVR causes DNA damage, leading to important mutations, mainly in proto-oncogenes and tumor-suppressor genes [15]. The greatest carcinogenic potential is in the ultraviolet B radiation spectrum, although ultraviolet A also acts as a cocarcinogen [16].

UVR acts cumulatively, inducing mutations in the *TP53* tumor-suppressor gene and compromising control of the cell cycle, leading to clonal expansion of neoplastic keratinocytes and induc-

ing cellular immunosuppression in a dose-dependent manner by interfering with neoplastic immunosurveillance [17–19].

Immunosuppression

In immunosuppressed individuals SCC is the most commonly detected skin cancer, with a 3:1 ratio compared with BCC, in contrast to the general population where ratio is of four BCCs to one SCC [20–23]. The longer the immunosuppression, the higher the risk of SCC development [24–26]. The higher incidence may be related to a decrease in the immunosurveillance.

Human Papillomavirus

A systematic revision showed, by gene amplification, that Human Papillomavirus (HPV) is more prevalent in lesional than nonlesional skin of patients with SCC and that SCCs in immunosuppressed patients have a higher prevalence of HPV compared with those of immunocompetent patients [27]. The HPV subtypes 6, 11, 16, and 18 are usually found in genital SCCs and type 16 in periungual SCC [28]. Failure to show an association between SCC and HPV in other studies suggests that more investigation is needed [29, 30].

Other Etiologic Factors

Other predisposing factors for the development of SCCs are genodermatoses (xeroderma pigmentosum) [15], chronic dermatoses (lichen sclerosus) [31], arsenic exposure [32], and ionizing radiation [31].

Clinical Presentation

SCC occurs preferentially in photoexposed regions, the most frequently affected being, in decreasing order, head and neck, extension surfaces of the hands and forearms, legs, shoulders, lower back, upper limbs, and other areas [33]. Its subtypes are as follows.
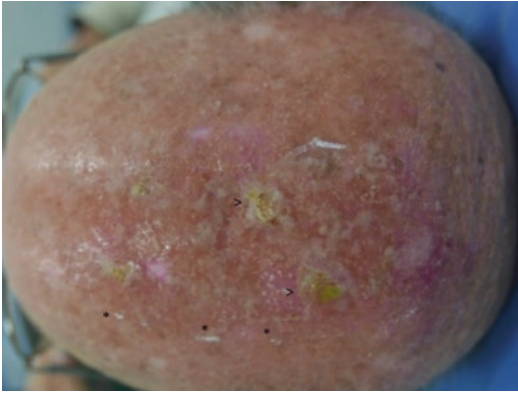
Fig. 15.1 Field of cancerization. Presence of multiple lesions of actinic keratosis (*asterisks*), photodamage, and palpable lesions of invasive SCC (*arrowheads*)

Actinic Keratosis

Actinic keratosis (AK), traditionally regarded as a preneoplastic condition, is now considered an intraepithelial form of SCC and the initial manifestation of a spectral disease concept, with a 0.1–20% risk of evolving into an invasive SCC [34, 35]. It presents clinically as erythematous papules or plaques with variable degrees of hyperkeratosis, resulting in thin scales or a warty aspect (hypertrophic actinic keratosis). In the lip region, especially the lower lip, it is called actinic cheilitis, presenting as a whitish plaque (leukoplakia), sometimes accompanied by fissures and erosions.

Multiple AKs are often found on photoexposed skin, with other signs of photodamage and lesions of invasive SCC. A region with clinical evidence of photodamage, multiple AK, and risk of developing SCC is defined as the field of cancerization (Fig. 15.1) [36–38].

SCC In Situ

In situ SCC, or Bowen's disease, is histologically characterized by atypical keratinocytes throughout the epidermal thickness, without dermal invasion. Usually asymptomatic, it presents as a papule that may progress to an erythematous plaque with variable scaly surface, which when detached can expose a red surface (Fig. 15.2). With time the lesion can be

Fig. 15.2 In situ SCC in the anterior thorax region manifesting as an erythematous, scaly plaque

more elevated with hyperkeratosis and crusts [39]. Discharge and symptoms such as pain and discomfort may be present in certain cases [33].

Bowen's disease can have peculiar presentations in intertriginous, periungual, and mucosal regions [40]. In situ SCC of the mucosal male genitalia, known as Queyrat's erythroplasia, manifests as an erythematous plaque with a velvety surface and delimitated margins, and sometimes erosion. Bowenoid papulosis is subtype of in situ SCC that occurs on the genital area, has a warty aspect, and is associated with some oncogenic HPV types such as 16 or 18 [41].

Invasive SCC

The evolution of lesions restricted to the epidermis into invasive SCC is defined clinically by the presence of infiltration as a solid consistency on palpation, at the base of the lesion. The clinical presentation can be a warty, hyperkeratotic plaque, sometimes ulcerated and having varying degrees of perilesional erythema (Fig. 15.3). Well-differentiated tumors present usually a hyperkeratotic crust, sometimes hypertrophic, characterized by cutaneous horn. Less differentiated lesions usually are ulcerated, with minor keratinized crust, being frequently found on the lips and genital areas [39].

When SCC occurs in an area of previous trauma or burn scar, it is known as Marjolin's ulcer (Fig. 15.4). This subtype shows aggressive behavior and a higher risk for local recurrence and metastases [42].

Fig. 15.3 SCC of the malar region manifesting as erythematous plaque with a keratotic surface
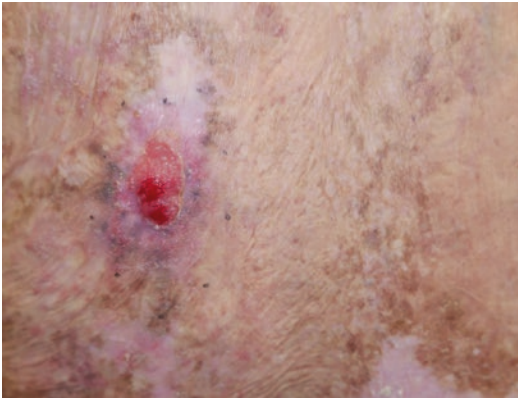
Fig. 15.4 Marjolin's ulcer. SCC in a burn scar area

Fig. 15.5 Type IV verrucous carcinoma

Verrucous carcinoma is a variant of SCC that develops in chronically irritated sites and shows a cauliflower-like exophytic growth with intense hyperkeratosis. It can be subdivided into four types [43]:

Type I: Flower-like oral papillomatosis (oral region)
Type II: Buschke–Loewenstein tumor (genital region)
Type III: Epithelioma cuniculatum (plantar region)
Type IV: Other regions (Fig. 15.5)

Cautious palpation of regional lymph nodes can detect regional metastasis or evidence of reactive inflammatory lymph nodes, the former presenting with a hard, irregular consistency, and sometimes adhering to adjacent structures [39].

Complementary Examinations

Anatomopathology

The anatomopathologic examination is central to the diagnosis, staging and classification of SCC. A lesion biopsy can be carried out with a scalp or punch, with attention paid to obtaining a sample that is representative of all skin layers, including the epidermis, dermis, and subcutaneous tissue.

The histologic findings are atypical keratinocyte proliferation with loss of polarization. When still restricted to one-third or two-thirds of the epidermis it is called AK, and is termed in situ SCC when the whole thickness of the epithelia is involved (Fig. 15.6). When the dermis is invaded
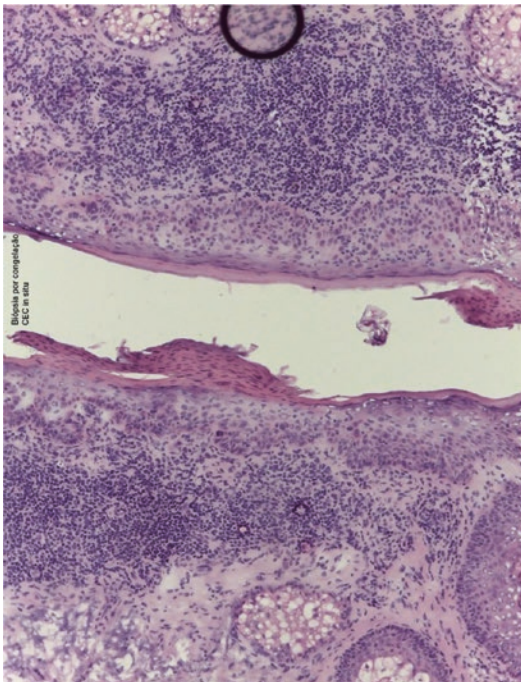
Fig. 15.6 Anatomopathologic examination displaying an in situ SCC (hematoxylin–eosin) (Courtesy of Dr. Lismary Mesquita)

Fig. 15.7 Anatomopathologic examination displaying a well-differentiated SCC (hematoxylin–eosin) (Courtesy of Dr. Lismary Mesquita)

it is known as invasive SCC. Other histopathologic characteristics are nuclear pleomorphism, apoptosis, atypical mitoses, and variable degrees of hyperkeratosis, parakeratosis, lymphocytes, plasmocytes, and histiocyte dermal infiltrates. Invasive SCC is classified according to the degree of differentiation: well differentiated (Fig. 15.7), moderately differentiated (Fig. 15.8), less differentiated (Fig. 15.9), and anaplastic or undifferentiated [39–41]. When perineural invasion is present it must be described in the pathology report, as well as the acantholytic and desmoplastic findings, as these aspects could influence clinical behavior.

Imaging Examinations

Complementary examinations are indicated in the staging of SCC when there is invasion of adjacent structures, such as deep soft tissues, cranial, axial, and appendicular skeleton, orbital content, parotid gland, auditory meatus, and

perineural infiltration; perineural invasion is an important prognostic factor in head and neck SCCs [44].

For the assessment of bone and soft tissue invasion computed tomography (CT) may be indicated, as well as in advanced disease located on the lower and upper limbs, where tendons, muscles, and bones may be involved. In patients with SCC that has developed in chronic cutaneous ulcers, the assessment of deep structures can be challenging; long-standing chronic inflammatory reactions could lead to scarring and subcutaneous fibrosis, and sometimes even adhesion to muscles or bones without necessarily being a result of tumoral infiltration. Imaging assessment or oriented biopsies could help to define whether to carry out conservative surgery or even a partial limb amputation [45].

If extension to head and neck structures is suspected, such as the orbit, the auditory meatus, the cranial base, intracranial extension, and perineural infiltration, nuclear magnetic resonance imaging (MRI) is preferred [46]. In specific cases

Fig. 15.8 Anatomo-pathologic examination displaying a moderately differentiated SCC (hematoxylin–eosin) (Courtesy of Dr. Lismary Mesquita)
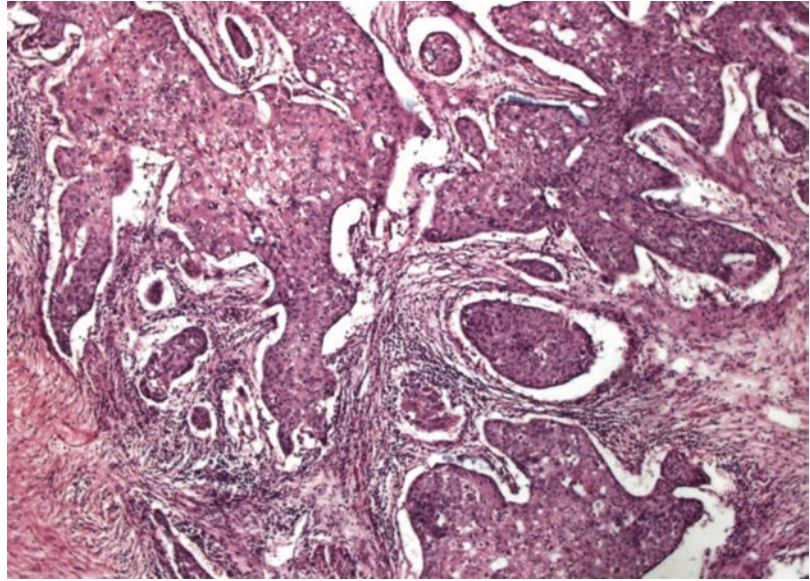
Fig. 15.9 Anatomo-pathologic examination showing a poorly differentiated SCC (hematoxylin–eosin) (Courtesy of Dr. Lismary Mesquita)
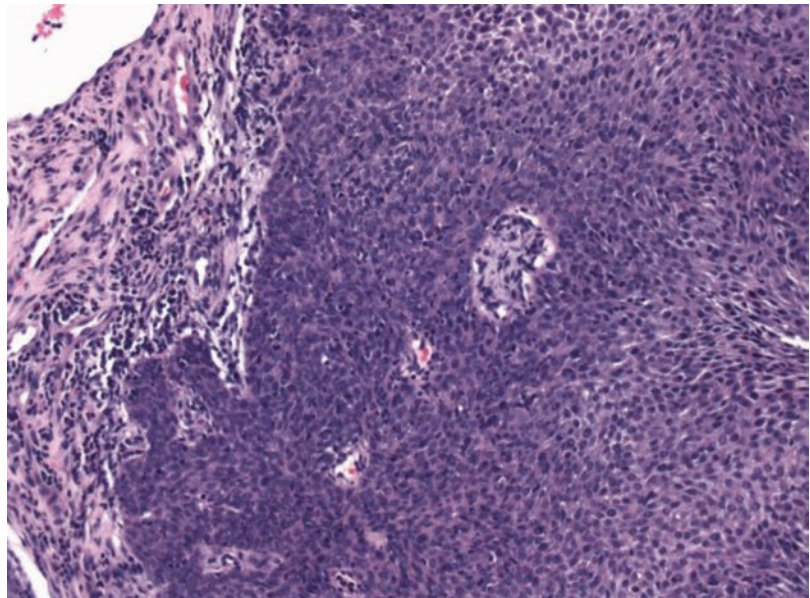
concerning the therapeutic strategy, as in more extensive facial or cranial resections, CT scan and MRI should be combined [47].

There is a greater risk of local recurrence when invasion of deep structures is present. The delimitation of surgical margins could be challenging because of the presence of scar and prior tissue movement resulting from previous surgery. Imaging analysis could help to define the deep extension of the relapsing disease.

When metastatic regional lymph nodes are clinically and radiologically suspected, fine-needle aspiration (FNA) biopsy or ultrasound-guided core biopsy (CB) helps in staging the lymph node status. In positive metastatic lymph nodes, radiographic assessment with CT or MRI of the involved nodal chain must be added to the assessment for the therapeutic plan. Clinical and radiologic reassessment should be carried out in cases with negative biopsies but clinical

suspicion. It is interesting to note that SCCs, especially when ulcerated with inflammatory reaction, could induce reactive lymph node enlargements that could be misinterpreted as metastatic lymph nodes. Careful evaluation is therefore necessary in this situation [48].

If distant metastasis is suspected, the lungs and bones being the most affected sites, thoracic and abdominal imaging studies are necessary for the correct staging, preferably using CT. In doubtful cases of the metastatic nature of the findings, positron emission tomography combined with CT may be indicated [49].

Thoracic and abdominal X-ray can be used when CT is not available, although these examinations are limited for small lung lesions and investigation of retroperitoneal lymph nodes.

Diagnosis

SCC diagnosis is mostly clinical, and histopathology will confirm the diagnosis and histologic subtype (Table 15.1).

The degree of differentiation is related to its biological behavior. Well-differentiated cells retain their cellular function, i.e., the ability to produce keratin, and will translate clinically into a more hyperkeratotic crust. Less-differentiated lesions will produce less keratin, showing their inability to exercise its paramount function, presenting usually as an ulcerated lesion. Palpation of regional lymph nodes is important for the cor-

Table 15.1 Diagnostic criteria for squamous cell carcinoma

1. *Clinical manifestations of the lesion:*
Erythematous-keratotic papule that may evolve into plaque with variable ulceration
Well-differentiated lesions tend to be more hyperkeratotic; less-differentiated lesions will show less keratotic and more hemorrhagic surfaces
Lymph node palpation for the correct staging
2. *Anatomopathologic examination:*
Confirmation of diagnosis by biopsy and definition of histologic risk factors
3. *Imaging examination:*
When deep structures and dissemination are suspected

Table 15.2 Differential diagnosis of epidermoid carcinoma according to the level of invasion

Actinic keratosis	Irritated seborrheic keratosis
	Benign lichenoid keratosis
	Porokeratosis
	Common warts
	Discoid lupus erythematosus
	Keratoacanthoma
	In situ SCC
In situ SCC	Superficial basal cell carcinoma
	Dermatitis
	Actinic keratosis
	Irritated or inflamed seborrheic keratosis
	Discoid lupus erythematosus
	Candidiasis
	Paget's disease
	Common warts
Invading SCC	Hypertrophic actinic keratosis
	Keratocanthoma
	Common warts
	Seborrheic keratosis
	Intradermal melanocytic nevus
	Pyogenic granuloma
	Eccrine poroma
	Deep mycoses
	Atypical fibroxanthoma
	Merkel cell carcinoma

rect staging. When deep invasion is suspected, because of adherence on palpation, imaging examinations may be useful.

Differential Diagnosis

The SCC differential diagnosis varies according to clinical type (Table 15.2).

Therapeutic Approach

The main goals of SCC treatment are: total removal of the tumor; minimizing the risk for recurrence and metastasis; preservation of normal tissue; and provision of the best possible functional and aesthetic outcome.

The therapeutic modality is based on the lesional classification of risk (Table 15.3),

Table 15.3 Risk factors associated with high risk SCC for local recurrence and metastases

Tumor characteristics
High-risk areas[a]: any size
Medium-risk areas[b]: >1 cm
Low-risk areas[c]: >2 cm
Ill-defined margins
Fast growth
Perineural invasion
Recurrence
Histology
Depth of invasion: >4 mm
Poorly differentiated
Aggressive pattern (acantholytic, desmoplastic fusiform cells SCC)
Perineural or vascular invasion
Patient aspects
Prior radiotherapy
Immunosuppression
Lesions in scars, chronic ulcers- or inflammation sites
Predisponent genetic syndromes (xeroderma pigmentosum)

[a]High-risk area: facial "H," auricular, pre- and postauricular, nose, temporal, eyelids, lip, chin, mandible, genitalia, hands, and feet
[b]Medium-risk area: cheeks, forehead, neck, scalp, and pretibia
[c]Low-risk area: trunk and limbs (except for the hands, feet, and pretibia) (Fig. 15.10)

approaching high-risk tumors with therapies of highest efficacy (Table 15.4). The first treatment is the best opportunity for cure and preservation of the normal tissue; subsequent approaches for affected margins or recurrences show worse cure rates and higher risks for metastases.

The gold standard and the most used treatment for SCC is surgery [50]. Topical nonsurgical treatments can be used in the cancerization field, in low-risk tumors, and in early-stage tumors such as AK and in situ SCC [51].

Topical therapies such as 5-fluorouracil (5-FU), imiquimod, ingenol mebutate, and photodynamic therapy are indicated in the treatment of field of cancerization, AK, and low risk in situ SCC located in low-risk areas. Local treatments are contraindicated for high-risk tumors [50].

Surgical procedures used for nonaggressive lesions include electrodesiccation and curettage, and cryotherapy. The proper use of these

High risk area
Medium risk area
Low risk area
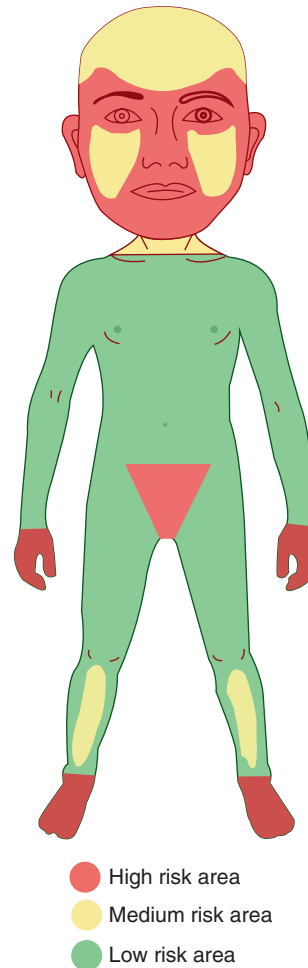
Fig. 15.10 Risk areas

techniques results in the local control of the disease in more than 90% of the cases [52]. These techniques should be avoided in hair-bearing areas (scalp, genitals, axillae, and beard) because of the risks of scarring alopecia and deep invasion.

Aggressive SCC usually shows ill-defined margins affecting the accuracy of the definition of surgical margins for the adequacy of tumor removal, especially in treatments such as conventional surgery, electrodesiccation and curettage, and cryotherapy. Another drawback of techniques such as cryosurgery, curettage, and electrodesiccation is the lack of specimen for histologic and margin assessment; these are therefore defined as blind methods.

Table 15.4 Clinical presentation of SCC and treatment modalities

	Treatment modalities
Actinic keratosis	Fluorouracil cream
	Imiquimod cream
	Ingenol mebutate gel
	Cryosurgery
	Curettage and electrocoagulation (electrodesiccation)
	Photodynamic therapy
In situ SCC	Fluorouracil cream
	Cryosurgery
	Curettage and electrocoagulation (electrodesiccation)
	Surgical excision
	Mohs micrographic surgery
Low risk SCC (trunk and limbs, except for the hands and feet, and pre-tibial)	**<1 cm**: Cryosurgery
	Curettage and electrocoagulation
	Surgical excision (4–6 mm margins)
	≤ 2 cm: surgical excision (4–6 mm margins)
High-risk SCC[a]	Mohs micrographic surgery
	Surgical excision (>6 mm margins)

[a]High-risk areas: any size; medium-risk areas: >1 cm; low-risk areas: >2 cm; ill-defined margins; fast growth; perineural invasion; recurrence; histology (depth >4 mm, less differentiated, aggressive pattern, perineural or vascular invasion), prior radiation sites; immunosuppression; scars, chronic ulcers, or inflammation sites; predisponent genetic syndromes

Recent review studies report good results for the surgical treatment of low-risk SCC treated with conventional surgery using 4- to 6-mm surgical margins, mainly in nonaggressive lesions, such as well-defined primary tumors less than 2 cm in diameter, and located in areas not including the ears, lips, eyelids, nose, and scalp and without invasion of the subcutaneous layer, showing cure rates of 95% [53–55]. Conventional techniques used for anatomopathologic sampling, such as the "bread-loaf section" or "cross-section," assess less than 5% of the specimen margins, increasing the risk of false-negative margins, especially in aggressive and infiltrative tumors [55]. The minimal surgical margins for high-risk tumors are 6 mm, or preferably the use of Mohs micrographic surgery (MMS), a surgical technique that yields the highest cure rates [56] The complete histologic margin control, the use of histographic mapping, and the possibility of staged excisions oriented by peroperative frozen pathology make MMS the treatment with highest cure rates for all kinds of SCC [57]. A comparative study showed that in primary SCCs the recurrence rate in 5 years was 3.1% for MMS against 7.9% for non-Mohs surgeries, and for recurrent SCCs 10% for MMS and 23.3% for non-Mohs surgeries [53]. SCC in burn scars, Marjolin's ulcer, recurrence of radiotherapy, solid organ transplant, less differentiated tumors, recurrent lesions, and lesions with positive surgical margins are indications for MMS [58, 59].

Radiotherapy is best reserved for patients at surgical risk and should be avoided in young patients (<50 years of age), owing to the risk of induction of a secondary cancer induced by the radiation. Aggressive SCCs have a 30% risk of perineural invasion, which increases the risk of recurrence and metastasis; in this setting postsurgical adjuvant radiotherapy should be considered.

Suspected regional lymph nodes must be investigated by FNA biopsy; in the presence of lymph node metastasis or highly suspected negative cases, lymphadenectomy of the affected chain is indicated. In head tumors, especially on the anterior scalp and ears, careful examination of the parotid region must be carried out to assess the risk for intraparotid lymph node metastatic involvement [60]; if present, partial or complete parotidectomy must be conducted, along with cervical lymphadenectomy [61, 62].

The use of postsurgical adjuvant radiotherapy of regional lymph nodes is indicated for multiple metastatic lymph nodes or extracapsular extension in the axillar and inguinal region [63]. Radiotherapy for cervical lymph nodes is indicated when two or more lymph nodes are affected or when there is extracapsular involvement [52, 64].

Follow-Up

All patients treated for SCC have to be followed-up for at least 5 years because of the risk for recurrence and development of other primary lesions.

Glossary

Acantholytic squamous cell carcinoma
   Variant of SCC characterized by a cleavage of the intercellular bridges, resulting in acantholysis.

Apoptosis   Programmed cell death.

Core biopsy   The removal of a tissue sample with a large needle for examination under a microscope.

Desmoplastic SCC   Variant of SCC characterized by a prominent trabecular growth pattern, narrow columns of atypical epithelial cells, and a marked desmoplastic stromal reaction.

Hyperkeratosis   Thickening of the stratum corneum, often associated with the presence of an abnormal quantity of keratin, frequently accompanied by an increase in the granular layer.

Leukoplakia   White patch or plaque of the mucosa and mucocutaneous junction.

Lichen sclerosus A chronic atrophic disorder mainly of the anogenital skin of females but also of males and of the general skin. Whitish, ivory or porcelain-white, sharply demarcated, individual papules may become confluent, forming plaques.

Nuclear pleomorphism   Marked variation of nuclear size, nuclear shape, or nuclear staining, a common finding in malignant lesions.

Parakeratosis   A disturbance of keratinization characterized by the retention of nuclei in the stratum corneum.

Photodamage   Skin changes consequent to exposure to the sun's ultraviolet radiation.

Positron emission tomography (PET)   A nuclear medicine, functional imaging technique that is used to observe metabolic processes in the body.

Punch biopsy   Use of a specialized surgical instrument (punch) for the removal of a full-thickness specimen of the skin (epidermis, dermis, and fat) in a defined area.

TP53 **tumor supressor gene**   Mutation of the *TP53* tumor suppressor gene is a frequent event in tumorigenesis; the many roles of the protein p53 as a tumor suppressor include the ability to induce cell cycle arrest, DNA repair, senescence, and apoptosis.

Xeroderma pigmentosum   A rare hereditary skin disorder caused by a defect in the enzymes that repair DNA damaged by ultraviolet light and resulting in hypersensitivity to the carcinogenic effect of ultraviolet light.

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Melanoma

16

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Key Points

- Melanoma is responsible for 75% of deaths from skin cancer and its incidence has rapidly been increasing
- Although the increasing incidence of thinner melanomas represents improved surveillance and earlier diagnosis, the overall mortality rate has not declined
- Dermoscopy and reflectance confocal microscopy are noninvasive techniques that increase accuracy in melanoma diagnosis and reduce unnecessary biopsies
- The definitive treatment of primary melanoma is wide local excision associated with sentinel lymph node biopsy when indicated
- The identification of genetic mutations has led to the development of target

drugs to better guide therapy for patients with advanced melanoma
- Advances in the understanding of immunologic mechanisms in melanoma have promoted the development of interventions with impact on clinical endpoints

Epidemiology

Melanoma incidence has rapidly been increasing over the past 50 years, especially in fair-skinned populations [47]. It is the second most diagnosed cancer among patients under 30 years old and one of the cancers with more years of productive life lost, representing a significant public health problem [122]. Even though it represents less than 5% of all cutaneous malignancies, because of its aggressiveness melanoma is responsible for 75% of deaths from skin cancer [117, 122]. When invasive, melanoma is the cutaneous tumor with the highest metastatic capacity, since it increases by 10% per millimeter of thickness [122].

Despite changes in attitudes toward increased recreational exposure to ultraviolet (UV) radiation, the current trend of increased melanoma is predominantly explained by an increasing incidence of thinner melanomas as a result of improved surveillance and earlier diagnosis [47].

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Annually this incidence increase varies between populations, ranging from 3% to 7%, with the highest rates in Australia and New Zealand, with up to 60 cases per 100,000 inhabitants per year [56, 102, 117]. In the United States, in the past 10 years the incidence of melanoma has been increasing an average of 2.6% each year [111]. In the age group older than 60 years, the estimated average annual percentage rate was 6.15% for the period between 1992 and 2005 [117].

Moreover, melanoma remains the only preventable cancer for which the mortality rate has not declined [103, 117, 122]. Mortality rates have remained relatively stable since the 1980s, which reflects improved survival due to earlier detection of thin melanomas at a curable stage, in view of the increasing incidence of the disease [117]. However, population-based studies have shown significant increases in tumors of all histologic subtypes and thicknesses, including thick melanomas (more than 4 mm), especially in older men [80, 114, 156]. The increase in incidence has been higher in men aged 65 years and older (five-fold in men versus three-fold in women), and mortality rates increased by 157% (from 7.5 to 19.3 per 100,000) among this age group [6, 57]. However, there is a trend toward a decrease in mortality in persons aged 20–44 years, by 39% (from 1.3 to 0.8 per 100.000) in women and by 29% (from 1.7 to 1.2 per 100.000) in men in the United States [57].

Fortunately, over the past 20 years overall 5-year survival has increased in the United States by nearly 91%, likely a result of earlier diagnosis [6]. The association between increased incidence of and survival for melanoma and stabilization of the mortality rate suggests overdiagnosis from increased early detection, either from screening or incidental detection [33].

Etiopathogenesis

Melanoma is a malignant neoplasm of melanocytic lineage that most frequently arises from melanocytes in the skin, but can also arise from autochthonous melanocytes from internal organs, including the central nervous system [14].

Although melanoma can arise from nevi, most primary melanomas do not show an associated precursor nevus [14].

Melanoma as a heterogeneous disease can present with different clinical, histopathologic, and biological aspects [121]. Most melanomas show an intraepithelial component, and the malignant cells are thought to initially proliferate along the basal layer (melanoma *in situ*) [14, 170]. After a period of months to years, the malignant melanocytes not only proliferate radially but also acquire the capacity to invade vertically into the dermis (invasive melanoma) [169]. However, lesions of intraepithelial origin are distinct from melanocytic neoplasms, which consistently lack epithelial involvement; these include uveal melanoma and intradermal melanocytic proliferations [14]. Nodular melanomas (NMs) lack substantial epidermal involvement and radial components, proceeding directly to vertical and rapid growth. Furthermore, NMs frequently present amelanotic coloration [103, 169] (Fig. 16.1).

Genetic profiles and molecular data have been identified for each of the different types of melanomas and have been correlated with distinct clinical and histopathologic aspects and biological behaviors of tumors [121]. Cutaneous primary melanomas usually present typical UV radiation–induced mutations in the mitogen-activated protein kinase (MAPK) pathway, with mutually exclusive driver mutations in BRAF, NRAS, c-KIT, GNAQ, or GNA11 [39]. Melanomas associated with intense, intermittent sun exposure (usually at the trunk and extremities) have high rates of *BRAF* (50%) or *NRAS* (20%) mutations. On the other hand, mucosal and acrolentiginous melanomas have lower rates of *BRAF* mutations (5–20%) and higher rates of *c-KIT* mutations (5–10%). Uveal melanomas usually show mutations in *GNAQ* or *GNA11* [39, 157, 158].
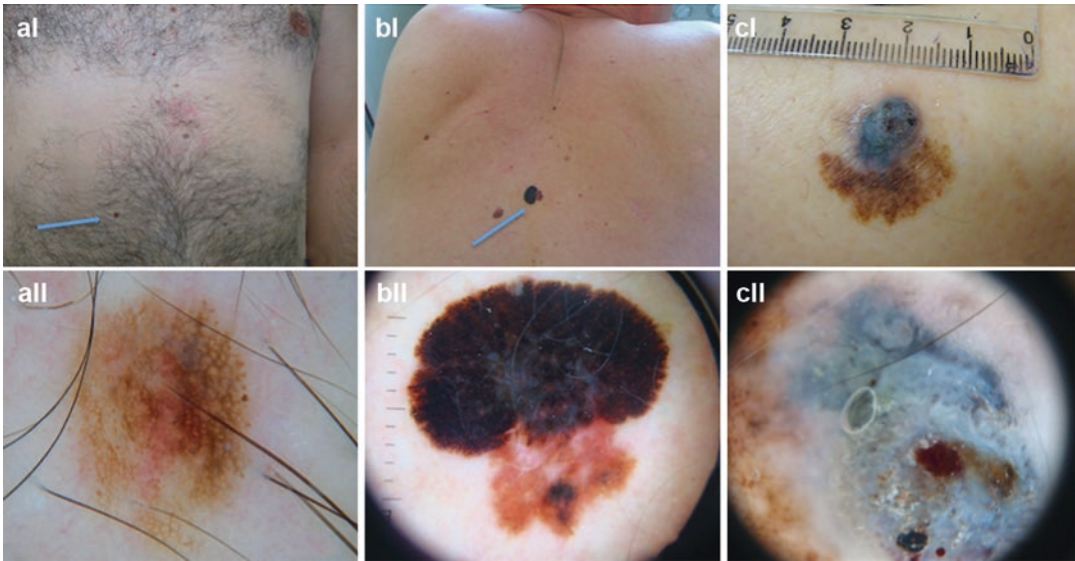
Fig. 16.1 Clinical and dermoscopic presentation of superficial spreading melanoma in three different evolutionary growth stages: incipient, radial growth, and vertical growth. (**aI**) Clinical image of a macular brown pigmented lesion on the abdomen (*blue arrow*). (**aII**) Dermoscopic image of an incipient (clinically featureless) superficial spreading melanoma presenting reticular pattern with atypical network and segmented clods and subtle bluish focal pigmentation. (**bI**) Clinical picture of a dark pigmented macular lesion on the back (*blue arrow*). (**bII**) Dermoscopic image of a superficial spreading melanoma in radial growth phase presenting an atypical network, radial lines and pseudopods, a blue-whitish veil, and structureless areas. (**cI**) Clinical picture of a macular-nodular pigmented lesion on the leg. (**cII**) Dermoscopic image of a superficial spreading melanoma in vertical growth phase presenting a peripheral atypical network and central diffuse blue-white pigmentation with ulcerated areas

Risk Factors

Melanoma etiology is complex and involves environmental, phenotypic, and genetic risk factors [122]. The main risk factors for developing cutaneous melanoma are described here.

Environmental Risk Factors
- Intense UV radiation exposure (e.g., sunburn history)
- Chronic, cumulative sun exposure
- Indoor tanning, especially in youth (before age 35 years)
- Immunosuppression (e.g., organ transplantation)

Phenotypic and Genetic Factors
- Phototype I (fair skin, inability to tan)
- Light hair (red or blond)
- Light eyes (blue, green, or gray)
- Increased common nevus count (>100 nevi)
- Atypical melanocytic nevus (>5 nevi)
- High density of freckles
- Premalignant and skin cancer lesions
- Actinic damage indicators (e.g., solar lentigines)
- Personal history of melanoma
- Family history of melanoma (≥1 affected first-degree relative)

Environmental Risk Factors

Exposure to UV radiation is the best-known exogenous risk factor for developing melanoma [6]. UV radiation causes DNA damage and induces melanoma carcinogenesis through the

formation of pyrimidine dimers, photoproducts, gene mutations, oxidative stress, inflammation, and immunosuppression [122]. Both intermittent, intense UV exposure (e.g., sunburn history) and chronic, cumulative sun exposure play a role in the pathogenesis of melanoma [54].

Melanomas developing in continuously sun-exposed areas such as the head and neck are more likely to be of the lentigo maligna melanoma subtype and to occur in older patients with a history of solar damage and nonmelanoma skin cancer. On the other hand, individuals with a high number of nevi tend to develop melanomas on intermittently sun-exposed body sites such as the trunk and extremities, mostly belonging to the superficial spreading melanoma or nodular melanoma histologic subtypes [54].

Indoor tanning is considered directly linked to the development of melanoma by the International Agency for Research on Cancer, which classified the whole UV spectrum and indoor tanning devices as carcinogenic to humans (group 1) [44, 53, 81]. A meta-analysis showed a 75% increase in the risk for melanoma (from 40% to 228%) when indoor tanning started during adolescence and young adulthood [20]. More recently a systematic review and meta-analysis found an association between use of sunbeds and a summary relative risk (RR) of 1.25 (1.09–1.43) for melanoma. This risk almost doubled (RR = 1.87) in youth (before age 35), with a 1.8% (0–3.8%) increase in melanoma risk for each additional session of sunbed use per year [20]. A 10-year follow-up study demonstrated that the daily use of sunscreen reduces the melanoma detection rate, suggesting that regular sunscreen use may prevent melanoma development and should be encouraged [64].

Besides UV exposure, other potential environmental risk factors are under study. Occupational exposure to pesticides was associated to a fourfold greater risk of melanoma compared with no occupational exposure (odds ratio [OR] 4.23, 95% confidence interval [CI] 1.94–6.31) [145]. Furthermore, indoor use of pesticides (four or more times per year) was associated with a 44% higher risk of melanoma (OR 1.44, 95% CI 1.11–3.49) [145].

Phenotypic and Host Factors

Melanoma occurs more frequently in Caucasians than other races. Phenotypic features associated with increased risk of melanoma are phototype (I vs. IV: RR = 2.09, 95% CI 1.67–2.58), skin color (fair vs. dark: RR = 2.06, 95% CI 1.68–2.52), hair color (red vs. dark: RR = 3.64, 95% CI 2.56–5.37), eye color (blue vs. dark: RR = 1.47, 95% CI 1.28–1.69), high density of freckles (RR = 2.10, 95% CI 1.80–2.45), presence of premalignant and skin cancer lesions (RR = 4.28, 95% CI 2.80–6.55), and actinic damage indicators (RR = 2.02, 95% CI 1.24–3.29) [54]. Ephelides and solar lentigines were shown to be independent risk factors for cutaneous melanoma related to sun exposure [54].

The number of melanocytic nevi represents a good predictor for cutaneous malignant melanoma, as the risk increases almost linearly with the number of common melanocytic nevi [18]. The presence of a high nevus count (more than 100 nevi) is associated with an almost seven-fold significant increased risk of melanoma compared with <15 nevi (RR = 6.89; 95% CI 4.63–10.25) [54, 127]. A high number of nevi on the arms may represent an increased total nevus count. People with 11–15 common nevi on the arms present an almost five-fold greater risk of melanoma than those with no nevi (RR = 4.82; 95% CI 3.05–7.62) [127].

Atypical nevi may play an independent role in melanoma risk, as the presence of five atypical nevi increases the risk ten-fold compared with the absence of atypical nevi (RR = 10.12; 95% CI 5.04–20.32) [54, 127]. Atypical nevi are usually larger than common nevi with a border not well defined, size 5 mm or more, color variegated, contour uneven, and presence of erythema [54].

Sporadic atypical melanocytic nevi outside the context of dysplastic nevus syndrome and/or familial melanoma are considered independent risk markers for sporadic melanoma [18].

Giant congenital nevi are also associated with increased risk, with a cumulative 5-year risk of cutaneous melanoma estimated at 5.7% [6, 41].

Persons with the atypical or dysplastic nevus syndrome (Clark nevus syndrome) present multiple atypical moles that continue to appear in adulthood and are at much higher risk of melanoma [54]. Individuals with atypical nevus syndrome and at least two family members with melanoma have a 500-fold increase in melanoma risk [127].

Personal or Family History of Melanoma and Genetic Factors

The presence of a history of melanoma or nonmelanoma skin cancer is associated with a three-fold relative risk of melanoma [6]. Personal history of melanoma increases 5–8% the risk of developing a second primary melanoma 49, 94, 122).

Approximately 5–10% of melanoma cases occur in a familial setting [122]. A family history of melanoma is considered positive if the patient has reported one or more affected first-degree relative [53]. Patients with a positive family history of melanoma have an RR of 1.74 compared with those with a negative family history [58].

In high-risk families, melanoma susceptibility is inherited following an autosomal dominant inheritance pattern with incomplete penetrance [19]. Multiple primary melanoma patients may also have inherited melanoma susceptibility and often present atypical mole phenotype [3, 20, 122, 126].

Two main genes are described as melanoma high-susceptibility genes: cyclin-dependent kinase inhibitor 2A (*CDKN2A*) and cyclin-dependent kinase 4 (*CDK4*). Germline CDKN2A mutations have been described in 20–50% of melanoma-prone families and in up to 15% of multiple primary melanoma patients irrespective of family history [62, 83]. However, the probability to have *CDKN2A* mutations in sporadic melanoma patients without personal or family history of melanoma is about 1% [122]. The penetrance for melanoma in *CDKN2A* carriers at the age of 80 years was reported to be 58% in Europe, 76% in the United States, and 91% in Australia [17]. Carriers of *CDKN2A* mutations also have an increased risk for developing pancreatic, breast, lung, and other tobacco-related cancers [21, 76, 123].

Another gene, the α-melanocyte-stimulating hormone (α-MSH) receptor 1 (*MC1R*), is considered a low to moderate gene risk and its variants are associated with skin and hair pigmentation. *MC1R* is one of the key regulatory genes in human pigmentation and is highly polymorphic in the Caucasian population [123]. The R variants are highly associated with red hair color phenotype (p.D84E, p.R142H, p.R151C, p.I155T, p.R160W, p.D294H) and are those most implicated with melanoma susceptibility. Carriers of two R alleles are at four- to six-fold higher risk of developing melanoma compared with individuals without these variants [123]. Recently it was shown that carriers of *MC1R* variants had increased melanoma risk independent of sun exposure [166].

Germline mutations in other genes such as breast cancer 1 (*BRCA1*) associated protein 1 (*BAP1*), telomerase reverse transcriptase (*TERT*), protection of telomeres 1 (*POT1*), and microphthalmia-associated transcription factor (*MITF*) were described in *CDKN2A* wild-type melanoma-prone families and may be responsible for a lower number of familial melanoma cases.

Genetic counseling and specific dermatologic follow-up should be offered to individuals belonging to melanoma-prone families or families with melanoma-related cancers (sarcoma, early-onset breast cancer, brain tumors, or pancreatic cancer) and/or with multiple primary mel-

anomas [128, 173]. Genetic testing should only be performed in individuals with at least a 10% chance of carrying a mutation before the test is done [7, 71].

Other Factors

There is an increase in incidence and poorer prognosis of melanoma in patients after organ transplantation associated with medical immuno-suppression. On the other hand, the scarcity of evidence does not permit us to establish a clear association between pregnancy or hormones and the risk or prognosis of melanoma [6]. Recently, a systematic review and meta-analysis showed increased risk of melanoma death (pooled hazard ratio [HR] 1.56, 95% CI 1.23–1.99) for pregnancy-associated melanoma compared with other melanomas, although this is debatable on a methodological level [26, 172].

Clinical Presentation

The World Health Organization (WHO) classification distinguishes four major clinical-histopathologic subtypes of melanoma: superficial spreading melanoma (SSM), NM, acral lentiginous melanoma (ALM), and lentigo maligna melanoma (LMM) [35, 65, 161]. Although these proposed categories represent distinct clinical and histopathologic presentations that are valuable for recognition and diagnosis, the impact of this classification on predicting prognosis and defining clinical management has been limited [18, 161].

SSM is the most frequent histopathologic subtype of melanoma in fair-skinned individuals [18]. It accounts for approximately 65% of all melanomas and the median age of diagnosis is between 40 and 60 years [18, 65]. SSM is most frequently seen on intermittently sun-exposed skin of the trunk of men and the legs of women, but may arise at any site. It usually begins as an asymptomatic brown to black mac-

ule with color variegation and irregular borders, sometimes also exhibiting pink discoloration. After a slow macular radial growth phase, a papular or nodular vertical growth phase develops (Fig. 16.1). Gray pigmentation and hypopigmentation are signs of regression associated with a host immune system response. Early-stage melanomas of ≤5 mm diameter may present asymmetry of pigmentation and borders [18].

NM represents around 20% of all primary melanomas diagnosed and often fails the ABCD categorization of suspicious lesions. The more aggressive biology of NM accounts for a shorter duration and advanced thickness of NM at presentation, and supports the importance of the "E" for evolution to the ABCD criteria [65]. Nodular melanoma usually presents as a black or blue nodule, sometimes pink to red (amela-notic), which may be ulcerated or bleeding (Fig. 16.2) [18].

Usually NM is firm and elevated with a history of fast growth. The acronym "EFG" (E = elevated, F = firm, and G = growing progressively for more than a month) indicates clinical clues for diagnosis [30, 60].

LMM represents approximately 10% of melanomas and usually develops in the seventh decade and later (Fig. 16.3) [18].

LMM occurs in chronically sun-exposed areas such as face and neck, and less frequently in the upper trunk and extremities [124]. Recognition of LMM in early stages is often difficult because its presentation can be quite subtle, and delayed diagnosis is common [124]. According to the English language literature, the entity is called "lentigo maligna" when it is confined to the epidermis (in situ) and as "lentigo maligna melanoma" when it invades the dermis. Currently it is generally believed that lentigo maligna and LMM belong to the same evolutionary spectrum, i.e., the same entity at different stages of development [124, 154]. In daily clinical practice, the diagnosis of facial lentigo melanoma may be a diagnostic challenge because of its similar clinical features to
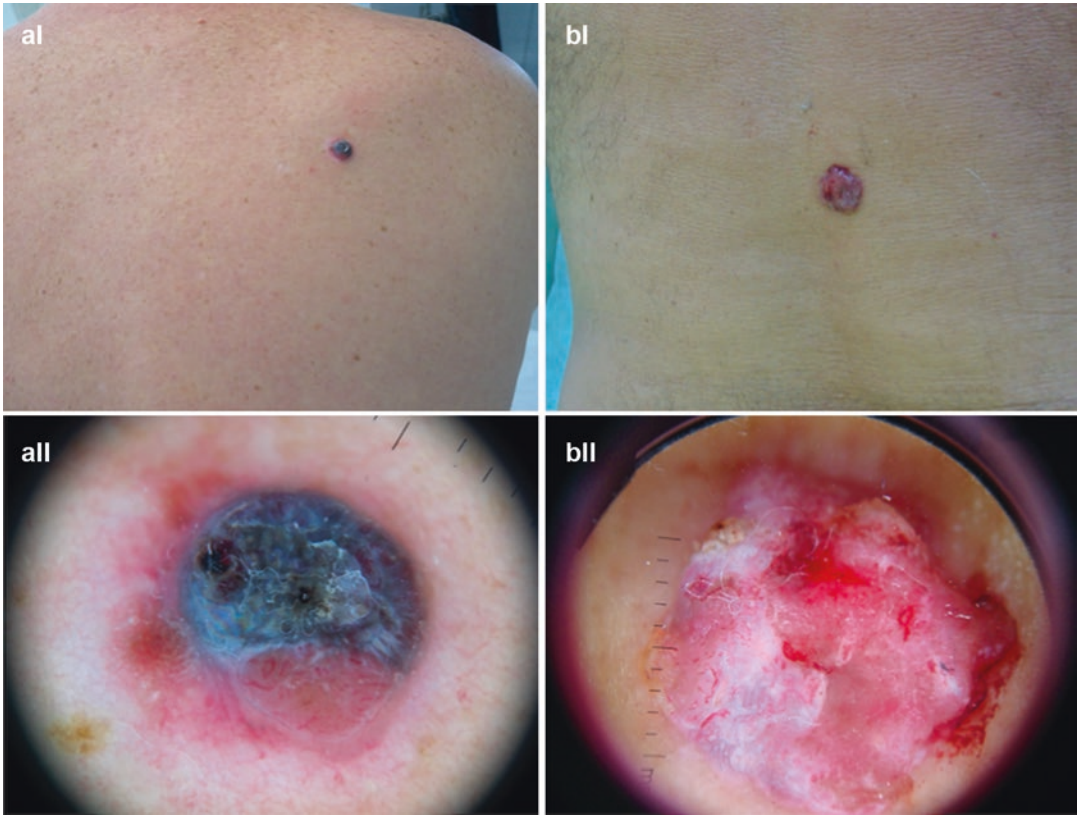
Fig. 16.2 Clinical and dermoscopic presentation of pigmented and amelanotic nodular melanoma. (**aI**) Clinical picture of a pigmented nodular lesion on the back. (**aII**) Dermoscopic image of a nodular melanoma presenting blue color, polymorphic vessels, shiny white streaks, and a small ulceration. (**bI**) Clinical picture of a nodular red tumor on the lumbar region. (**bII**) Dermoscopic image of an amelanotic melanoma presenting white and red colors, atypical linear and dotted vessels, and large ulcerated areas

other lesions such as solar lentigines and pigmented actinic keratosis [2].

ALM is an infrequent subtype of melanoma arising on the palms, soles, and nail apparatus. It represents approximately 5% of all melanomas and up to 70% of melanomas diagnosed in black individuals. At acral sites melanoma typically presents as an asymmetric brown to black macule with color variation and irregular borders (Fig. 16.3). ALM may be amelanotic and are easily misdiagnosed as verrucae or other benign conditions [18].

NAM is rare and accounts for 0.18–2.8% of all melanomas. The relative incidence of NAM among Africans and Asians is much higher than that found among Caucasians [132]. Melanoma mainly arises from the nail matrix but it is also found in the nail bed and lateral folds [132]. NAM of the nail matrix can present as longitudinal pigmentation (also known as melanonychia striata longitudinalis), as shown in Fig. 16.3. Early pigmented nail-unit melanoma is characterized by brown background associated with longitudinal lines that are irregular in color, width, spacing, and parallelism. Nail melanoma may also present as a black background with areas of different hue of pigmentation, with barely visible lines. About 20–30% of cases of NAM are amelanotic [132]. When arising in the nail bed NAM presents as a nodule that can be
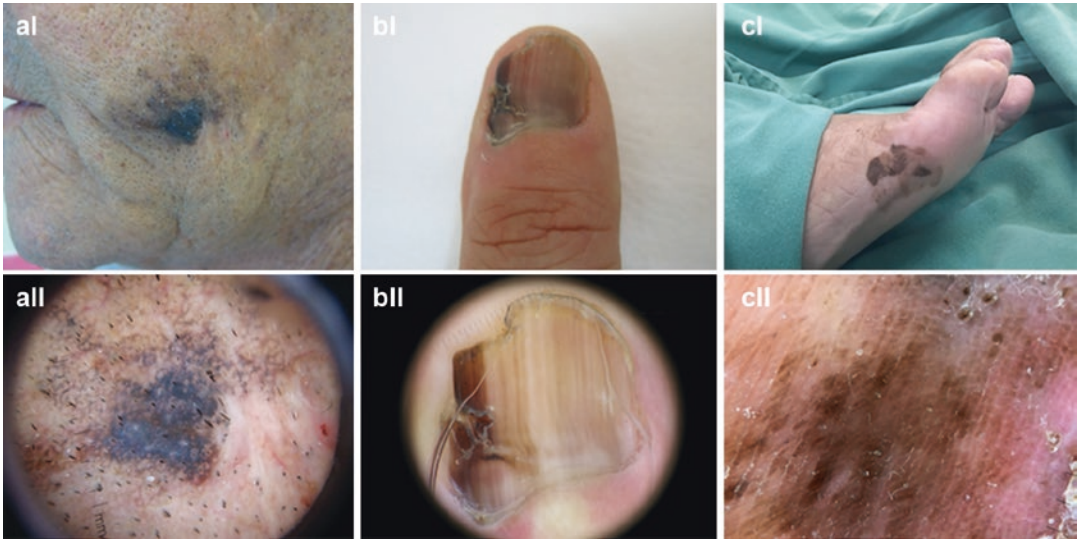
Fig. 16.3 Clinical and dermoscopic picture of melanoma at special sites: facial, nail, and acral. (**aI**) Clinical picture of a macular brown-black macule on the face. (**aII**) Lentigo maligna melanoma showing annular-granular pattern with gray dots, asymmetric pigmented follicular openings, rhomboidal structures, and obliterated hair follicles. (**bI**) Clinical picture of a melanonychia striata longitudinalis on the index finger. (**bII**) Dermoscopy shows a nail apparatus melanoma with brown background of pigmentation and irregular pattern of the longitudinal microlines that are irregular in color, thickness, and spacing; there is also erosion of the nail plate with dystrophy. (**cI**) Clinical picture of a black- to brown-colored pigmented patch on the lateral plantar region. (**cII**) Dermoscopy of an acral lentiginous melanoma with parallel ridge pattern and irregular diffuse pigmentation

ulcerated and bleeding with partial destruction of the nail plate. The use of the "ABCDEF" rule was suggested to evaluate suspicious melanonychia: A stands for "age, Asian and African American"; B for "brown, black, breadth, and borders"; C for "change or absence of change, despite adequate treatment"; D for digits (thumb, hallux, index finger); E for extension of pigment (Hutchinson sign); and F for familial history of melanoma [97]. The Hutchinson sign describes the presence of pigment on the proximal, lateral, or distal fold, which represents the radial growth phase of subungual melanoma.

Mucosal melanomas account for approximately 1.3–1.4% of all melanomas. In early stages mucosal melanoma presents clinically as brown-black macules with shades of gray, sometimes with multifocal distribution. Advanced mucosal melanomas usually develop black to dark brown nodules combined with the macular part at the base of a tumor [79].

Less prevalent melanoma variants with distinct clinical-epidemiologic presentations are spitzoid, nevoid, desmoplastic, malignant blue nevus, and ocular melanoma.

Diagnosis

Melanoma diagnosis is a constant challenge in clinical practice, since it represents a potentially fatal skin cancer and the prognosis is strictly related to early detection.

Clinical recognition is classically associated with the ABCD(E) mnemonic of melanoma, which was designed to provide simple criteria for early diagnosis by physicians and general population. Friedman et al. [52] published the ABCD acronym (asymmetry, border irregularity, color variegation, diameter >6 mm). The letter E (for evolution) was subsequently added in order to include some tumors that could be missed by

other criteria, especially small and nodular melanomas. Clinicians and patients should be attentive to changes (evolving) of size, shape, color, and symptoms such as itching or bleeding [1, 61, 75, 133]. The EFG rule stands for an Elevated, Firm, or Growing lesion and helps to identify amelanotic and nodular melanomas, which are often clinically symmetric and uniform in color.

Another important clinical clue for suspicious lesions is the "ugly duckling sign." In a person with multiple nevi, lesions tend to resemble one another. A mole that deviates from that nevus pattern should be carefully analyzed [66, 144]. The main concepts regarding melanoma diagnosis are described in Box 16.1.

Box 16.1 Diagnosis of Cutaneous Melanoma

Clinical presentation: ABCDE rule (asymmetry, border irregularity, color variegation, diameter >6 mm, evolution/ evolving); nodular melanoma: EFG rule (elevated, firm, growing)

Dermoscopy: noninvasive technique that increases accuracy in melanoma diagnosis

Total-body photography and digital dermoscopy: used for surveillance of high-risk patients, allowing diagnosis of "featureless" melanomas, while minimizing unnecessary biopsies

Reflectance confocal microscopy: noninvasive technique that allows the skin evaluation at cellular level and quasi-histologic resolution, improving diagnostic accuracy for melanoma and reducing unnecessary excisions

Histopathology: excisional biopsy and histopathologic evaluation is the gold standard for melanoma diagnosis

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Dermoscopy

Incipient melanomas often do not fulfill some of the clinical ABCD criteria [141]. Dermoscopy increases sensitivity in the clinical diagnosis of melanoma from 60% to up to 90% [4]. It has been proved by three meta-analyses to be more accurate than naked eye examination for the diagnosis of cutaneous melanoma [8, 87, 160], and is now widely accepted by dermatologists in routine tumor screening. This noninvasive and low-cost technique allows the recognition of morphologic structures not visible to the naked eye, allowing the detection of clinically unsuspected lesions. Besides the proven value in differentiating benign and malignant melanocytic lesions, it is also very useful in the differential diagnosis with nonmelanocytic melanoma simulators such as pigmented basal cell carcinoma, which have specific dermoscopic features that can lead to a straightforward diagnosis [104].

Multiple algorithms were created and validated to guide the differentiation between benign and malignant melanocytic lesions and help in the decision to perform a biopsy, including the ABCD rule, Menzies method, the seven-point checklist, pattern analysis, and more recently Kittler's algorithm based on pattern analysis. Pattern analysis is the preferred method by experienced dermatologists and has the same sensitivity with higher specificity [4]. This method describes global and local features to be analyzed. Global patterns related to melanoma are multicomponent (association of three or more dermoscopic structures), atypical starburst or starburst pattern in adults, atypical reticular, atypical globular, and nonspecific pattern. Local features that should raise concern for melanoma are atypical pigmented network, irregular dots, globules, streaks or blotches, atypical vessels, and blue-white structures (including blue-white veil and regressive structures).

Total-Body Photography and Digital Dermoscopy

Despite the great benefit provided by dermoscopy, there remains a small proportion of difficult-to-diagnose melanomas that could require a different approach for recognition. Incipient melanomas may lack dermoscopic features specific to this disease [86, 125], and patients can present multiple clinically and dermoscopically atypical nevi, sometimes impossible to distinguish from early melanomas [15, 106]. Total-body photography (TBP) and digital dermoscopy (DD) are the most reliable
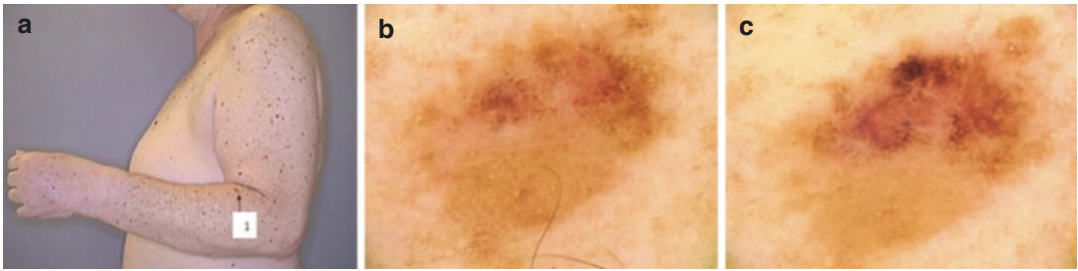
Fig. 16.4 Clinical and dermoscopic picture of an incipient melanoma detected by digital dermoscopy follow-up. (**a**) Clinical picture of a high-risk patient with increased nevus number and atypical melanocytic nevi (dysplastic nevus syndrome). Atypical melanocytic lesion on the left forearm (*arrow*) is followed by digital dermoscopy. (**b**) Dermoscopic image shows a predominant reticular pattern at baseline with discrete white network and irregular clods. (**c**) The same lesion at 8-month follow-up developed focal hyperpigmentation, dotted vessels, and accentuated white network; the diagnosis of an early invasive melanoma (Breslow 0.4 mm) was confirmed on histopathology

approaches to detect initial melanoma in high-risk patients [139, 140]. TBP consists of baseline body photographs for follow-up comparison that facilitate the detection of new and changing lesions. This information is very important, as it is well known that melanoma often develops de novo in clinically normal-appearing skin rather than in pre-existing melanocytic nevus [164]. DD allows the capture and storage of the dermoscopic images and its monitoring over time, enabling the detection of subtle changes associated with melanoma (Fig. 16.4).

A meta-analysis of digital follow-up demonstrated that this technique allows the diagnosis of "featureless" melanomas, recognized only because of changes [142], while minimizing unnecessary biopsies, since stable atypical lesions are considered benign and can be followed without excision.

Reflectance Confocal Microscopy

Recently, reflectance confocal microscopy (RCM) has been introduced in dermatologic research to provide important additional information in equivocal melanocytic lesions [59, 120]. This noninvasive technique allows skin evaluation at the cellular level and quasi-histologic resolution with histopathologic correlation. Many studies have demonstrated that RCM is particularly useful as a second-level examination of doubtful lesions selected by dermoscopy or DD

[69, 101], increasing sensitivity and avoiding unnecessary biopsies.

Histopathology

Melanoma diagnosis is established by histopathologic examination. Atypical melanocytes are seen singly and in small nests in the epidermis and papillary dermis in radial growth phase, and characteristically atypical cells show upward (pagetoid) migration in multiple layers within the epidermis. In situ lesions are confined to the epidermis. In the vertical growth phase nests/nodules of malignant melanocytes expand further into the reticular dermis and beyond. Numerous mitotic figures often are noted and there is absence of maturation at deeper levels of the dermis.

Breslow tumor thickness (depth of invasion in millimeters), ulceration and mitotic rate are the three most important characteristics of the primary tumor for predicting outcome [9] and should always be mentioned. It is also recommended for the pathology report to include deep and peripheral margin status, microsatellites, pure desmoplasia if present, and Clark (invasion) level for nonulcerated lesions 1 mm or less where mitotic rate is not determined. Microsatellitosis is defined as the presence of tumor nests greater than 0.05 mm in diameter, in the reticular dermis, subcutaneously, or vessels beneath the principal invasive tumor but separated from it by at least 0.3 mm of normal tissue [116].

Some melanocytic lesions can be very challenging and simulate melanoma histopathologically, requiring evaluation by an experienced pathologist, as in the case of atypical nevi and spitz nevi, recurrent, traumatized and UV-exposed lesions, and specific locations such as genital and acral nevi.

Immunohistopathology

Immunohistochemical stains usually are not necessary for diagnosis of cutaneous melanoma, but can be useful in difficult cases to help the differentiation from benign lesions and especially from nonmelanocytic tumors. S-100 is the most sensitive marker for melanocytic lesions, although not specific, and HMB45 is highly specific but has limited sensitivity. Ki67 is a proliferation marker and can help to distinguish nevi from melanoma [118].

Complementary Examinations

Although there is scarce epidemiologic data regarding the use of laboratory and imaging tests in the initial evaluation of melanoma patients, they may be necessary to accurately stage patients prior to definitive treatment [34]. The general approach according to clinical/pathologic stage is summarized in Table 16.1.

Differential Diagnosis

Differentials to consider in the diagnosis of malignant melanoma include many melanocytic and nonmelanocytic conditions, as follows:

Melanocytic:
- (Atypical) Melanocytic nevi
- Spitz nevi
- Blue nevi
- Combined nevi
- Recurrent nevi
- Congenital nevi
- Halo nevi

Table 16.1 Imaging and laboratory evaluation for workup of cutaneous melanoma according to stage

Stage	Evaluations
0 (in situ)	Routine imaging or laboratorial tests are not recommended
I–II	Baseline chest X-ray
	CT and PET/CT scan: limited value for detecting unsuspected visceral metastases in asymptomatic patients
	Imaging tests only to evaluate specific signs and symptoms
III	Baseline imaging for staging and to evaluate specific signs and symptoms:
	CT of the chest and abdomen
	PET/CT in high-risk patients: may be preferred if available
	Bone scans: have not had any clinical value in asymptomatic patients
IV	Baseline imaging for staging and to evaluate specific signs and symptoms:
	LDH serum levels
	MRI of the brain and CT of the chest, abdomen, and pelvis
	PET/CT: patients who have solitary or oligometastatic disease, where the issue of surgical resection is more relevant

CT computed tomography, *PET* positron emission tomography, *LDH* lactate dehydrogenase, *MRI* magnetic resonance imaging

- Ink-spot lentigo
- Melanosis of mucosal regions

Nonmelanocytic
- Basal cell carcinoma
- Bowen's disease
- Seborrheic keratosis
- Pigmented actinic keratosis
- Thrombosed hemangioma, angiokeratoma
- Paget's disease
- Metastatic tumors to the skin
- Adnexal tumors
- Pyogenic granuloma
- Dermatofibroma
- Dermatofibrosarcoma protuberans
- Kaposi's sarcoma
- Subungual hematoma
- Black heel (hemorrhage in stratum corneum caused by trauma)
- Tinea nigra

Staging

The staging system is essential for the best therapeutic choice, owing to the strong correlation between the clinical and pathologic characteristics with the prognosis. In 2017, the American Joint Committee on Cancer (AJCC) 8th Edition updated the TNM staging system [1, 2] (Tables 16.2 and 16.3 [171]).

Therapeutic Approach

Surgical Treatment of Cutaneous Melanoma

Despite the clinical advances in the differentiation of a suspicious lesion on skin, biopsy is required for the evaluation of histology and determining the diagnosis [55, 134]. The treatment of cutaneous primary melanoma is fundamentally surgical. After initial biopsy, the definitive treatment of primary melanoma is wide local excision associated with sentinel lymph node biopsy (SLNB) when indicated. It is important to note that the surgery in two stages is a key concept in the treatment of cutaneous melanoma.

Excisional Biopsy

Excisional biopsy is considered the gold standard in the diagnosis of cutaneous melanoma [155]. It consists of complete resection of suspicious skin lesion, usually through a fusiform incision with scant side edges (2 mm), including the subcutaneous tissue. The analysis of the completeness of the primary tumor is the most accurate way for the recognition and evaluation of the microstaging criteria, especially the depth of invasion (Breslow), which is the most important factor in defining the prognosis (chance of lymph node and systemic involvement) and final resection margins [5, 36].

The incision in the trunk, head, and neck, generally elliptical, must be directed toward the skin tension lines (Langer's lines) to facilitate subsequent surgical treatment (margins of expansion), reaching improved functional and cosmetic results [82, 155]. In the limbs the guidance should be longitudinal, following and preserving the

Table 16.2 TNM staging system for cutaneous melanoma according to AJCC 2017

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Melanoma in situ
T1	≤1 mm
T1a	Without ulceration and <0.8 mm in thickness
T1b	<0.8 mm in thickness with ulceration or 0.8–1.0 mm in thickness regardless of ulceration
T2	1.0–2.0 mm
T2a	Without ulceration
T2b	With ulceration
T3	2.0–4.0 mm
T3a	Without ulceration
T3b	With ulceration
T4	>4.0 mm
T4a	Without ulceration
T4b	With ulceration
Regional lymph nodes (N)	
NX	Regional nodes cannot be assessed
N0	Absence of lymph node involvement
N1	One tumor involved lymph node or in-transit, satellite, and/or microsatellite metastasis with no tumor-involved nodes
N1a	One clinically occult (detected by SLNB)[a]
N1b	One clinically detected
N1c	In-transit, satellite, and/or microsatellite metastasis with no tumor-involved node
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastasis with one tumor-involved node
N2a	Two or three clinically occult (detected by SLNB)[a]
N2b	Two or three, at least one of which was clinically detected
N2c	One clinically occult or detected with in-transit, satellite, and/or microsatellite metastasis
N3	Four or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastasis with two or more tumor-involved nodes or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastasis
N3a	Four or more clinically occult (detected by SLNB)[a]
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes with in-transit, satellite, and/or microsatellite metastasis

Table 16.2 (continued)

Distant metastasis (M)	
M0	No distant metastasis
M1	Evidence of distant metastasis
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node
M1a(0)	LDH level not elevated
M1a(1)	LDH level elevated
M1b	Distant metastasis to lung, with or without M1a sites of disease
M1b(0)	LDH level not elevated
M1b(1)	LDH level elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a, M1b, or M1c sites of disease
M1c(0)	LDH level not elevated
M1c(1)	LDH level elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease
M1d(0)	LDH level not elevated
M1d(1)	LDH level elevated

lymphatic path, preventing loss in detection of SLNB and allowing a less complex subsequent definitive intervention [155].

Incisional Biopsy

In extensive lesions in specific locations (face/distal end) and in those with low index of suspicion for melanoma, where complete removal can cause serious sequelae, incisional biopsy may be indicated [82, 151, 155]. The removal of a fragment of skin lesion containing part of the tumor with positive lateral margins should reach the subcutaneous tissue and include the thicker or darker area, sometimes selected by dermoscopy. Technically it may be realized with a scalpel through an elliptical incision or "punch." However, it has been shown that the Breslow index (BI) is underestimated in a significant number of cases of incisional biopsy [19].

Shave Biopsy

There are two distinct types of shave biopsy: in the first, the withdrawal of a portion of the skin lesion into the dermis with a straight sharp blade positioned at 45° to the epidermis (incisional) is indi-

Table 16.3 Stage groupings for cutaneous melanoma

Stage	Clinical staging[a] T	N	M	Stage	Pathologic staging[b] T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	Any T	N1, N2, N3	M0	IIIA	T1a, T1b or T2a	N1a or N2a	M0
				IIIB	T0	N1b or N1c	M0
					T1a, T1b or T2a	N1b/c or N2b	M0
					T2b or T3a	N1a-N2b	M0
				IIIC	T0	N2b, N2c, N3b or N3c	M0
					T1a–T3a	N2c or N3(a,b,c)	M0
					T3b, T4a	Any N > N1	M0
					T4b	N1a–N2c	M0
				IIID	T4b	N3 (a, b, c)	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

[a]Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases
[b]Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy.

cated in the diagnosis of benign skin tumors or when the suspicion of melanoma is low [115, 116]. The second, called saucerization, consists in complete removal of the lesion with a straight blade and convex borders with lateral margins of at most 2 mm, reaching adipose tissue (excision) [134]. The latter technique is accepted as part of the procedure to diagnose cutaneous melanoma [116].

Fine-Needle Aspiration

Fine-needle aspiration is an accurate method for the diagnosis of possible metastatic lesions of cutaneous melanoma, but except in rare situations should not be used to confirm the primary tumor [36, 155]. Although this procedure is able to precisely identify the presence of melanoma, it does not allow the evaluation of relevant information such as the thickness (Breslow), ulceration, and so forth. This technique is valuable for the identification of subcutaneous metastases, soft tissue, and clinically positive nodes, with a high accuracy of 92.1% sensitivity and 99.2% specificity [112, 135].

Biopsy of Special Sites

Melanocytic lesions suspicious located on the mucosal surfaces of the oral or genital cavity should be biopsied by the same techniques as those for the skin. Because of the vascularity of these regions, careful local hemostasis should be performed after the procedure.

In suspected cases of ungual melanoma one fusiform excision biopsy is recommended, being narrow, longitudinal, and extending deep into the periosteum. Thus, information is obtained from all elements of the nail unit: proximal nail fold, matrix, bed, and plate [131]. Pigmentation on the matrix provides valuable guidance during surgery, although it is not always present. To minimize the subsequent nail dystrophy biopsy, repositioning of the lateral margins should always be carried out. The use of a "punch" can be advantageous when there is a chance of nail matrix melanoma. This procedure is performed with or without avulsion of the ungual plate [13].

Treatment of the Primary Lesion

In the definitive surgical procedure with wide local excision, all layers of the skin to the muscle fascia should be removed (deep margin) [143]. With respect to radial margins, in melanomas in situ the recommended removal is 0.5 cm in complex areas (e.g., on the face) at 1 cm from the lesion or site of

Table 16.4 Surgical margins for wide excision of primary melanoma

Tumor thickness	Recommended margins
In situ	0.5–1 cm
≤1.0 mm	1 cm
>1–2 mm	1–2 cm
>2–4 mm	2 cm
>4 mm	2 cm

Adapted from NCCN [116]

biopsy [5, 116]. In tumors of thickness up to 1 mm, the lateral margin recommended is 1 cm [36]. In tumors of thickness 1–2 mm, a resection margin of 1 cm (e.g., on the face) to 2 cm is recommended [116, 159]. Above 2 mm of tumor thickness it is established that 2 cm is adequate. In thick tumors ≥4 mm, a 2-cm excision margin is appropriate (Table 16.4).

Local recurrences are considered recurrences within 2 cm of the scar from the primary melanoma excision. Local recurrence is reported to be strongly associated with the development of in-transit, regional, and distant metastasis [18].

Sentinel Lymph Node Biopsy

This technique is used in an attempt to show early lymph node metastases (micrometastases), identifying which individuals need to undergo radical surgery of the lymph nodes and who will benefit from adjuvant systemic treatment. SLNB is considered the standard of care in evaluating the staging and prognosis of patients with cutaneous melanoma in whom there is a substantial risk of regional node metastasis [70, 147].

As the BI is the main factor associated with SLNB positivity, patients with in situ melanoma (Stage 0) should not undergo SLNB. For patients with melanoma under 0.76 mm and no factors for increased risk of nodal involvement such as ulceration of the primary tumor, a mitotic rate ≥1/mm^2, or lymphovascular invasion, SLNB is not indicated. In the rare event that a conventional high-risk feature is present in melanomas ≤0.75 mm, the decision regarding SLNB should be considered on an individual basis. In patients with melanoma Stage IA that are 0.76–1.0 mm thick with

no ulceration and mitotic rate <1 per mm^2, the recommendation is not fully uniform (most guidelines do not recommend the procedure, although the NCCN latest update enters the possibility to be discussed with the patient). For patients with Stage IB or II melanoma (0.76–1.0 mm thick with ulceration or mitotic index ≥1 and/or lymphovascular invasion or >1.0 mm, any feature), SLNB is recommended [116, 163, 167]. For patients with thick tumors (>4 mm) SLNB provides prognostic information, regional disease control, and identification of candidates for adjuvant therapies.

The procedure has three distinct phases: lymphoscintigraphy, radio-guided detection of the ganglion, and pathologic evaluation of the specimen. In the first step, conducted in the nuclear medicine sector, identification of the path of lymphatic drainage is made by intradermal injection around the scar of previous biopsy of a radioactive contrast agent (technetium-99m and phytate, or dextran or sulfur colloid) for identification of the nodal basis [149]. In a second step, an intradermal injection of a bluish dye (isosulfan blue or patent blue) is realized intraoperatively for 10–20 min before the incision in the area previously identified by lymphoscintigraphy. After this time, with the aid of a probe that detects radiation (gamma-probe), it proceeds to location of the labeled node. The injection of the radiopharmaceutical added to the blue substance allows the location of the lesion in 98% of cases [27]. The third phase comprises the histologic and immunohistochemical evaluation of the surgical specimen.

The risk of a positive result on SLNB in melanomas 1.01–2.0, 2.01–4.0, and ≥4.01 mm in size is approximately 12%, 28%, and 44%, respectively [138]. In patients with melanoma 0.75–1.0 mm thick, the positivity of SLNB is around 6.2% [116]. The prognostic significance of SLNB and its impact in survival was accessed by the Multicenter Selective Lymphadenectomy Trial I (MSLT-I) [110]. SLNB was confirmed as a prognostic tool for patients with intermediate (1.2–3.5 mm) and thick (>3.5 mm) melanomas. The melanoma-specific survival rate at 10 years was significantly worse in patients with a positive lymph node biopsy than in those with a negative lymph node biopsy [110]. Although for the overall study population no treatment-related difference

in the 10-year melanoma-specific survival was shown, the 10-year melanoma-specific survival rate was significantly improved in patients with intermediate-thickness melanomas (1.20 to 3.50 mm) found to have nodal metastases who underwent SLNB and immediate lymphadenectomy compared with those initially managed with observation followed by treatment when they developed clinical disease. More recently, the international trial MSLT-II has shown that in patients with melanoma and sentinel-node metastasis the immediate completion lymphnode dissection increased the rate of regional disease control at three years but did not increase melanoma-specific surviva l, which contrasts with MSLT-I results [179] . It is possible that a survival benefit with early surgery occured among patients with disease that was limitated to the sentinel node and in MSLT-II it was not seen due to a dilution of therapeutic effect, since the majority of the study population did not have melanoma in nonsentinel nodes

If SLNB is negative, regional lymph node dissection is not indicated. Patients with positive SLNB (Stage III) should undergo a complete lymph node dissection of the involved nodal basin with risk of additional positive nonsentinel nodes in 18% of cases [116].

Clinically Detectable Regional Lymph Nodes

Complete regional lymphadenectomy is the first-line therapy for patients presenting positive nodes proved by clinical examination, cytology (fine-needle aspirate), or histology (lymph node biopsy) without radiologic evidence of distant metastases [162]. Surgical management in this setting is associated with improved long-term disease-free survival and decreased morbidity caused by mass effect from involved nodes [116]. The prognosis of patients with lymph node metastasis varies with the number of positive lymph nodes, their presentation (micro- or macrometastasis), and characteristics of the primary lesion (thickness, ulceration, and mitosis). Therefore, the surgical approach provides an accurate staging in addition to local control of the disease.

Locoregional Advanced or Metastatic Disease

Melanoma usually metastasizes first to lymph nodes and then to secondary sites such as skin, subcutaneous soft tissue, brain, and lung. Metastatic spread is mainly regional in about 70% of patients, presenting as rapidly growing lymph nodes or as in-transit metastasis [18]. Cutaneous metastasis appears as a dermal nodule or plaque, more often in the proximity of the primary tumor. In-transit metastasis is defined as intralymphatic tumor in the skin or subcutaneous tissue more than 2 cm from the primary tumor but not beyond the nearest regional lymph node basin [116].

Surgical indication may have curative intent (completely resectable) or be palliative (quality of life). For individuals who have unresectable disease, an isolated limb perfusion (ILP) or isolated limb infusion (ILI) are alternative treatments with the intention of avoiding amputation. These techniques consist in treatment of the affected limb with regional chemotherapy (with melphalan) associated with hyperthermia, keeping it isolated from the rest of the body by a tourniquet [16, 153]. Another method is electrochemotherapy, a nonsurgical procedure used for palliation in patients unable to undergo ILP or ILI with unresectable lesions or metastases in transit (cutaneous and/or subcutaneous) [85, 108]. By this method the output of electrical pulses through electrodes placed on or near lesions increases cell membrane permeability; it is associated with intravenous chemotherapy, usually bleomycin and cisplatin [152]. In selected patients with Stage IV melanoma, when the molecular biology is favorable, the "performance status" is adequate, and the lesions are completely resectable, surgery may be indicated.

Adjuvant Treatment

Adjuvant therapy aims to improve the cure rate for melanoma patients who have already undergone a definitive surgical procedure. Various strategies have been tested over the years, including chemotherapeutic (such as cyclophosphamide and dacarbazine) and immunotherapeutic

agents [10, 148]. However, consistent benefit in overall survival in unselected melanoma patients has never been detected. Risk stratification and case individualization seems to be the best approach in adjuvant treatment for melanoma.

There is no benefit of adjuvant treatment in melanoma patients with BI ≤0.75 mm, without ulceration, and mitotic activity <1 mm^2. Cases with BI >0.76 mm and ≤4 mm, or BI <0.75 mm with ulceration or mitotic activity ≥1/mm^2 were studied in low-dose interferon-α (IFN-α) trials with different treatment durations. Although increased disease-free survival was observed [6–8], adjuvant treatment indication remains controversial in this scenario and observation or inclusion in clinical trials remain a viable, and usually preferred, option [67, 74, 119].

Predictive factors such as BI larger than 4 mm, presence of ulceration, and regional node involvement are strongly associated with a higher risk of local and systemic recurrence. This population was enrolled in trials of IFN-α at higher doses. In the ECOG 1684 trial, patients were randomly assigned to 1 year of high-dose IFN-α2b (20 million units/m^2 5 days per week for 4 weeks followed by 10 million units/m^2 subcutaneously three times weekly for an additional 11 months) or close observation. An increase in relapse-free survival (median 1.7 versus 1.0 years) and prolongation in median survival (3.8 versus 2.8 years) in the IFN-α group was detected. In a subsequent analysis with extended follow-up, the overall survival improvement in the treatment arm was no longer statistically significant [89, 90].

The Intergroup E1690 study compared high-dose IFN-α with low-dose IFN-α or observation only. The eligibility criteria for this study were similar to those for ECOG 1684, except that patients with clinically normal regional nodes were not required to undergo staging lymph node dissections. There was a significant increase in relapse-free survival for high-dose IFN-α in comparison with the observation group (HR = 1.28). Again, no overall survival benefit associated with high-dose IFN-α was observed [88].

IFN-α exposure is associated with significant rates of toxicity and the consequent need of dose reductions and treatment discontinuation. Fatigue, depression, myelosuppression, thyroid

dysfunction, and liver failure are among the more prevalent clinical manifestations. Systematic laboratory and clinical monitoring should be carefully pursued. Strategies such as the use of pegylated forms of IFN-α were tested in an attempt to address this issue. The EORTC 18991 study used 6 μg/kg weekly subcutaneously for 8 weeks (induction) followed by 3 μg/kg weekly subcutaneously up to 5 years (maintenance) and showed an increase in disease-free survival, particularly in the microscopic nodal disease subgroup (N1) [43].

For patients with impaired macroscopic or multiple lymph nodes (N2 and N3), there is meta-analytic proven benefit with adjuvant high doses of IFN-α. A meta-analysis that included 14 studies with a total of 8,122 patients compared the use of IFN-α with observation only, placebo, or GM2-KLH vaccine (considered inactive). This survey demonstrated increased disease-free survival (HR with recurrence 0.82, 95% CI 0.77–0.87) and overall survival (HR for death 0.89, 95% CI 0.83–0.96) with IFN-α treatment [109]. The adjuvant IFN-α at high doses consist of an induction phase of 20 million units/m^2 intravenously 5 days a week for 4 weeks followed by a maintenance phase with 10 million units/m^2 subcutaneously three times a week for an additional 11 months based on the ECOG 1684 trial [90].

Recently, ipilimumab, an anti-CTLA4 monoclonal antibody, was approved by the US Food and Drug Administration for adjuvant therapy. This approval was based on the EORTC 18071 clinical trial. The study included stage III patients and compared placebo with ipilimumab. With a mean follow-up of 2.7 years, an increase in relapse-free survival (HR 0.75, 95% CI 0.64–0.90) was detected. Long-term monitoring is still necessary to assess the impact on overall survival. Furthermore, it is important to emphasize the significant treatment-related toxicity: 90% of the patients had some immune-related effect. Moreover, five cases of death were related to the treatment with ipilimumab [42]. Trials comparing IFN-α and ipilimumab are currently in progress (ECOG 1609, NCT01274338).

Radiation therapy may have a role as adjuvant therapy after primary surgery for melanomas, but is associated with a higher rate of local recurrence despite adequate excision, such as those with positive margins. Adjuvant radiotherapy after lymph node dissection can also be considered when factors that impact negatively on local control (such as extranodal tumoral extension) are present. Data showing a decreased rate of local occurrence is available, but no difference in improved overall survival was detected [25, 68]. Thus there is no routine indication for the use of adjuvant radiotherapy in unselected cases and treatment should be individualized, considering margins and lymph node dissection findings.

Palliative Treatment

For many years, cytotoxic chemotherapy had been widely used as the main therapeutic strategy in patients with advanced melanoma. Although response rates were associated with chemotherapy exposure, no schedule has demonstrated an increased overall survival. Nowadays, with advances in immunotherapy and molecularly targeted therapy, the roles of chemotherapy are restricted to later treatment lines.

There is no consistent clinical benefit with single-agent versus combination chemotherapy. The agent most commonly used in patients with metastatic melanoma is dacarbazine [38]. Temozolomide, fotemustine, platinum compounds, vinca alkaloids, and taxanes also have experimental data describing limited activity [50, 150]. Combinations including cytotoxic agents and interleukin-2 and/or IFN-α (biochemotherapy) were previously evaluated with promising results, but with limited incorporation into routine clinical practice because of frequent and severe toxicity and the need for complex and intensive clinical management [48, 82].

The identification of genetic mutations on the genesis of melanoma and the understanding of the role of MAPK pathway activation have led to the identification of several target drugs and a paradigm shift in advanced melanoma treatment over the last decade. Molecular targets such as BRAF, MEK, RNA, and KIT were evaluated, and many predictors are being routinely used in the initial workup of patients with advanced melanoma as a tool to aid better therapy guidance.

BRAF mutations are found in approximately 50% of patients with cutaneous melanoma, and are more frequent in young patients and skin lesions without chronic sun damage [39, 40, 105], The presence of a V600 BRAF mutation predicts a higher response to BRAF and/or MEK therapeutic inhibition. Clinical activity of vemurafenib, dabrafenib, trametinib, and cobimetinib is being described by clinical trials in this scenario.

Vemurafenib is a potent inhibitor of BRAF. It was compared with dacarbazine in a phase III trial and showed increased overall survival (13.6 vs. 9.7 months, HR 0.70, 95% CI 0.57–0.87) [31, 107]. QT interval prolongation was described, requiring electrocardiogram monitoring. Sun-exposure avoidance and careful skin examination is mandatory since photosensitivity reactions and a high risk of cutaneous squamous cell carcinoma were strongly associated with vemurafenib use.

Dabrafenib is another inhibitor of BRAF that showed activity in patients with advanced melanoma BRAF V600E mutation. Dabrafenib was compared with dacarbazine and showed increased progression-free survival (6.7 vs. 2.9 months, HR 0.35, 95% CI 0.20–0.61) [73]. Preliminary assessment on updated data from the study showed promising results regarding overall survival benefit [72].

Trametinib is a MEK inhibitor initially evaluated in combination with dabrafenib in an attempt to retard the development of resistance BRAF inhibition. The COMBI-d trial showed that the combination led to an increased progression-free survival (median 11.0 vs. 8.8 months, HR 0, 67, 95% CI 0.53–0.84) and a tendency toward better overall survival. Furthermore, there was a reduction in the cutaneous toxicity incidence rate with the combination approach [51, 99]. Other studies have shown similar results [100, 136]. The vemurafenib–cobimetinib (a MEK inhibitor) combination was also tested, with a similar increase in disease-free survival, improvement in response rate, and tendency to increase overall survival compared with single-use vemurafenib [91, 95].

Advances in the understanding of immunologic mechanisms in melanoma tumorigenesis and progression also promoted the development of interventions capable of inducing significant impact on clinically useful endpoints. Ipilimumab is a monoclonal antibody directed against cytotoxic T-lymphocyte antigen 4 (CTLA-4) tested in clinical trials in the second line following chemotherapy or in combination with dacarbazine. Increased survival was observed in both settings [78, 137, 168]. As observed with many similar immunologic interventions, a slower pattern of response rates and a protracted clinical course of the disease, with longer periods of stable tumoral volumes, may be observed. In this setting, palliative surgical resections can be considered using an individualized approach.

Anti-PD1 antibodies, such as pembrolizumab and nivolumab, are one of the most recent therapeutic innovations in advanced melanoma care. Pembrolizumab showed increased progression-free survival and objective response rate in patients previously refractory to ipilimumab [130]. Similarly, when compared directly with ipilimumab, greater progression-free survival and overall survival was observed with pembrolizumab [136]. Nivolumab demonstrated increased overall survival in treatment-naive patients when compared with chemotherapy and an increased response rate in patients previously treated with ipilimumab [136, 165]. In addition, the combined administration of nivolumab and ipilimumab showed a higher response rate than these agents used alone, and mature overall survival data are promising [95]. Pharmacoeconomics concerns, long-term toxicities, optimal management of acute adverse effects, and the development of an optimal treatment sequence based on clinical and molecular stratification remain challenging issues in this rapidly changing scenario.

Follow-Up

Although the prognostic impact of a systematic follow-up approach, in particular with the introduction of new adjuvant interventions, is debatable, the early detection of a resectable locoregional recurrence or a second primary melanoma may lead to a more favorable outcome. The possibility of introducing any of the highly active new interventions before organ dysfunction secondary to metastatic disease may also represent a theoretical goal. Consensus recommendations tend to rely on clinical history and physical examination, saving laboratory tests (particularly serum lactate dehydrogenase) and

Table 16.5 Follow-up for cutaneous melanoma stages I to III

Stage	Evaluations
0 (in situ)	Clinical history and physical examination every 6–12 months during the first 5 years and every year after 5 years
	Routine imaging or laboratorial tests are not recommended
I	Clinical history and physical examination every 4–6 months during the first 2 years, then every 6 months for 5 years and every year after 5 years
	Routine radiologic imaging is not recommended
II	Clinical history and physical examination every 3 months during the first 2 years, then every 6 months for 5 years and every year after 5 years
	Consider routine LDH, chest X-ray, CT, brain MRI, and/or PET/CT scans every 3–12 months for up to 5 years
III	Clinical history and physical examination every 3 months during the first 2 years, then every 6 months for 5 years and every year after 5 years
	Routine LDH, chest X-ray, CT, brain MRI and/or PET/CT scans every 3–12 months for up to 5 years

Consider routine radiologic imaging in Stage ≥IIB according to [116]

CT computed tomography, *PET* positron emission tomography, *LDH* lactate dehydrogenase, *MRI* magnetic resonance imaging

imaging studies for patients at high risk of recurrence (Table 16.5) [29, 116] (Ryan et al. 2011).

Regional lymph node ultrasonography may be considered in Stage IB or higher and/or in patients with an equivocal lymph node physical examination or in whom SLNB was not possible (or not successful), according to the availability and accessibility of the method (grade of recommendation C) [29, 116].

Dosage of S100 protein serum levels may be valid in Stage IB or higher as a progression marker if available (level of evidence C) [29].

Prognosis

According to AJCC Melanoma Staging Database, among patients with T1 melanomas the 10-year survival rate was 92%, while it was 80% in T2

patients, 63% in T3 patients, and 50% in T4 patients. Five-year survival rates for Stage III were 78%, 59%, and 40% for patients with Stage IIIA, IIIB, and IIIC melanoma, respectively. In the absence of nodal metastases, patients with intralymphatic metastases have 5-year survival rates of 69%. One-year survival rates among Stage IV patients were 62% for M1a, 53% for M1b, and 33% for M1c melanomas [9].

Prevention and Screening

There is no consensus as to whether screening in the general population for melanoma is likely to be effective in reducing mortality, owing to the absence of randomized trials. However, there is current evidence that melanomas detected by the physician are thinner than those detected by patients or family members and that access to and the use of a dermatologist are correlated with a better prognosis [22, 46, 58, 146].

Based upon the available evidence, it is reasonable to recommend to high-risk individuals with a family history or presence of multiple and/or atypical moles to undergo at least annual full-body skin examination for routine screening of melanoma by a trained physician.

For the general population, educational measures such self-examination and careful observation of the skin may be encouraged. Clinicians should remain vigilant for skin lesions during routine or opportunist visits.

The "ABCD Rule" has been shown to be a valuable tool for teaching patients to identify changes that suggest melanoma. Trained people were more often able to diagnose melanoma than those who did not receive any information about the ABCD Rule [112].

Prevention measures for cutaneous melanoma are:

- Avoiding artificial tanning (tanning beds)
- Avoiding excessive sun exposure
- Wearing sunscreen and protective clothing
- Participating in skin cancer education programs
- Being familiar with the A, B, C, D, and E signs of melanoma
- Close monitoring of any changes in skin examination and seeking medical care

- Patient-based skin self-examination and periodic physician-based total-body skin examination are recommended in patients with multiple and/or atypical nevi
- Individuals at high risk (e.g., with many atypical nevi) may use TBP and DD for surveillance
- The strategy of prophylactic excision of all atypical melanocytic nevi in patients with multiple lesions is not proven to decrease risk

Glossary

Confocal microscopy Noninvasive technique using a confocal laser microscope that allows in vivo evaluation at cellular level and quasi-histologic resolution, improving diagnostic accuracy of melanocytic and nonmelanocytic skin lesions and reducing unnecessary excisions.

Dermoscopy Noninvasive technique that increases diagnostic accuracy of melanocytic and nonmelanocytic skin lesions using a magnifier polarized or nonpolarized light source.

Dysplastic nevus Atypical nevus or Clark's nevus. Melanocytic lesions that are larger than 5 mm, have irregular shape, indistinct borders, and variable pigmentation. Histologic features include disordered growth pattern, random cytologic atypia of melanocytes, and lymphocytic host response.

Sentinel lymph node The first lymph node or group of nodes draining the tumor site.

Target molecular therapy Drugs that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") that are involved in the growth and spread of cancer.

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Cutaneous T-Cell Lymphoma and NK Cells

Lisia Nudelmann and Renan Rangel Bonamigo

Key Points
- Primary cutaneous lymphomas are a group of extranodal non-Hodgkin lymphomas characterized by accumulation of lymphocytes on skin
- Approximately 75–80% of PCLs are classified as cutaneous T-cell and natural killer (NK) cell lymphomas (CTCL/NK)
- Mycosis fungoides corresponds to approximately 44% of all LPC
- The following factors should be considered in the etiology of CTCL: genetic, environmental, and infectious

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Introduction

Primary cutaneous lymphomas (PCLs) are a group of extranodal non-Hodgkin lymphomas characterized by early accumulation of mononuclear cells, most of them lymphocytes, on skin, with no evidence of extracutaneous disease at diagnosis [1–4].

Epidemiology

PCL has an annual incidence estimated at between 0.3 and 1 per 100,000 inhabitants in North America and western Europe. Skin is the second extranodal locale most affected by lymphoma after the gastrointestinal tract. Approximately 75–80% of PCLs are classified as cutaneous T-cell lymphomas (CTCLs) and natural killer (NK) cell lymphomas, with an absolute predominance of mycosis fungoides (MFs), which corresponds to approximately 44% of all PCLs [2–9].

Etiopathogenesis

The etiology and the exact steps in the pathogenesis of CTCLs are not understood. It is more reasonable to assume that these diseases represent the end point of several different processes. The following factors should be considered in the etiology of CTCL [10].

Genetic Factors Including Chromosomal Abnormalities

The pathogenesis of CTCL is characterized by altered immune biology and the accumulation of cytogenetic abnormalities during disease progression, including increased transcription factor activity, such as amplification of JUNB, which is involved in T-cell proliferation, differentiation, and apoptosis [11, 12].

Changes in a number of tumor-suppressor and apoptosis-related genes (such as *p16*, *p15*, *p14*, *PTEN*, *p53*, *JunB*, *HLA-G*, *Fas*, Fas ligand, and *Nav3*) have been recorded in patients with MFs, Sézary syndrome (SS), and other CTCLs, although how most of these alterations affect T-cell behavior is still not clear [13]. In 50–85% of patients with MFs and SS who were tested, one frequent genetic abnormality seems to interfere with expression of NAV3, which might act as a tumor suppressor in T cells [14].

In addition to multiple defects in apoptosis, aberrant cell-cycle regulation, including inactivation of the CDKN2A-CDKN2B locus, is frequently observed in CTCLs [9]. Cyclin upregulation, including cyclin D1, and loss of RB1 have also been described [9, 15].

Furthermore, clonal T-cell receptor gene rearrangements are detected in most cases of CTCL [16, 17].

Environmental Factors

CTCL occurs more often than expected in immune-suppressed patients [18]. Transplant patients sometimes develop lymphomas, 30% of which are CTCLs, and these prognoses seem to be worse [19]. In addition, a number of CTCL cases have been described in the setting of human immunodeficiency virus [18, 20].

Furthermore, studies suggested associations of CTCL with industrial exposures, suggesting the role of environmental factors in triggering disease carcinogenesis. Subsequent case-control studies designed to explore such hypotheses have yielded mixed results. Some have failed to pro-

vide evidence for relationships between occupational, recreational, or chemical exposure history and development of CTCL [18]. By contrast, a multicenter European study showed that employment in the paper, glass, pottery, and ceramics industries [21] and occupational exposure to halogenated hydrocarbons [22] were associated with increased MF risk. However, such investigations have been difficult to execute and are complicated by the low prevalence of CTCL.

Infectious Factors

Numerous studies have illuminated the impact of human T-cell leukemia virus (HTLV) type 1 in the pathogenesis of adult T-cell leukemia/lymphoma (ATLL) [23, 24].

It has been proposed that antigens related to the Epstein–Barr virus (EBV) may be driving this abnormal interaction in CTCL, especially extranodal NK/T-cell lymphoma, nasal type [25–27]. Other members of the Herpesviridae family, such as human herpesvirus, also have been reported in patients with MF and parapsoriasis. A superantigen effect associated with *Staphylococcus aureus* has been proposed, based on the increased usage of V-beta families associated with *Staphylococcus* in MF cells as well as nonclonal T cells in MF lesions [28]. Other investigators have made associations between MF and SS, and the common cytomegalovirus.

Classification

The current classification for PCLs was proposed in 2005 by the World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC). This was the first classification that was accepted and used worldwide by pathologists, oncologists, hematologists, dermatopathologists, and dermatologists. According to this classification, PCLs were subdivided into NKTCL, cutaneous B-cell lymphoma (CBCL), and neoplasia of hematologic precursor [29]. In 2008 the WHO updated this classification with a few modifications of terminology [30] (Box 17.1).

> **Box 17.1 WHO-EORTC Classification for Primary Cutaneous T- and NK-Cell Lymphomas**
>
> Mycosis fungoides (MF)
>
> MF variables and subtypes
>
>   Folliculotropic MF
>
>   Pagetoid reticulosis
>
>   Granulomatous cutis laxa
>
> Sézary syndrome
>
> Adult T-cell leukemia/lymphoma
>
> Primary cutaneous CD30+ lymphoproliferative diseases
>
>   Primary cutaneous anaplastic large cell lymphoma
>
>   Lymphomatoid papulosis
>
>   Subcutaneous panniculitis-like T-cell lymphoma
>
>   Extranodal natural killer/T-cell lymphoma, nasal type
>
> Primary cutaneous peripheral T-cell lymphoma, unspecified
>
>   Primary aggressive epidermotropic CD8+ cutaneous T-cell lymphoma (provisional entity)
>
>   Cutaneous γδ T-cell lymphoma (provisional entity)
>
>   Cutaneous lymphoma of small and medium pleomorphic CD4+ T-cell (provisional entity)

Cutaneous T-Cell Lymphomas

Mycosis Fungoides

Clinical Presentation

MF usually affects adults, with an average age at diagnosis between 55 and 60 years old, but it may also occur in children and adolescents [11, 16, 31].

There is a predilection for male patients (2:1) [4, 11, 16, 25, 31]. It is more common in black persons (2:1) and less frequent in Asian and Hispanic individuals [4, 25].

Clinically, MF is characterized by patches, plaques, and/or tumors, which are usually erythematous and brownish [32, 33], with initial preference for covered areas of the body, such as buttocks, torso, and breasts [11, 16] (Figs. 17.1, 17.2, and 17.3). Other variables include the hypopigmented, hyperpigmented, vesicular, pustular, bullous, and granulomatous forms. MF is associated with follicular mucinosis, with or without alopecia, ichthyosis, and lichenoid-like pityriasis [4, 25, 32, 34–36].
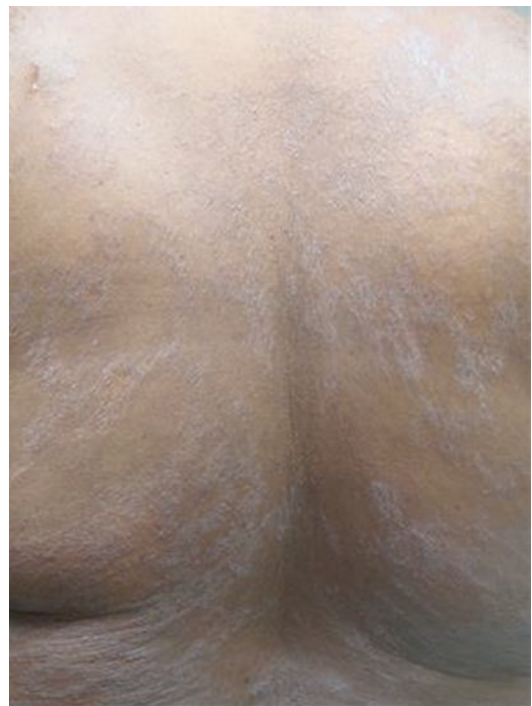
Fig. 17.1 Erythematous and squamous plaques in a patient with mycosis fungoides

MF d'emblée is defined by the appearance of tumors without pre-existing lesions [32, 37]. Some authors argue that this can be a form of peripheral T-cell lymphoma, not MF [4, 16, 19].

Hypopigmented MF is characterized by lesions that may clinically resemble tinea versicolor, pityriasis alba, vitiligo, leprosy, sarcoidosis, and postinflammatory hypopigmentation. Although the patient may have only hyperpigmented lesions, the presence of concomitant erythematous lesions is common [25, 36].

Granulomatous cutis laxa is characterized clinically by large erythematous plaques that coalesce to form loose and hanging skin folds,

Fig. 17.2 Erythematous plaque in a patient with mycosis fungoides

similar to cutis laxa, located in intertriginous areas, such as inguinal regions and armpits or flexion areas [16, 19, 32, 38].

Folliculotropic MF is a variant whereby patients may have patches and plaques of classical MF, but hardened plaques, nodules, or tumors can also occur simultaneously, usually on the head and neck, with associated alopecia, since there is preference for the hair follicles. It mainly affects adults, but occasionally can occur in children and adolescents. Men are more frequently affected. Keratotic follicular papules, acneiform lesions, cysts, and comedones may be present in the lesion or perilesionally. As the disease progresses, bulky tumor masses occur [16, 17, 19, 34, 39].

Pagetoid reticulosis is by definition an MF variant restricted to cases with erythematous and scaly, solitary, well-circumscribed, slow-growing, lesions usually on the extremities [11, 16, 19, 29]. Extracutaneous dissemination or deaths related to the disease, contrary to classical MF, have not been reported [16].

Complementary Examinations

Histopathologic Examination

MF is characterized, in the stage of plaques, by a dense superficial infiltrate, frequently in band or lichenoid, of small lymphocytes, with atypical

Fig. 17.3 Tumoral mycosis fungoides

Fig. 17.4 Epidermotropism in a patient with mycosis fungoides
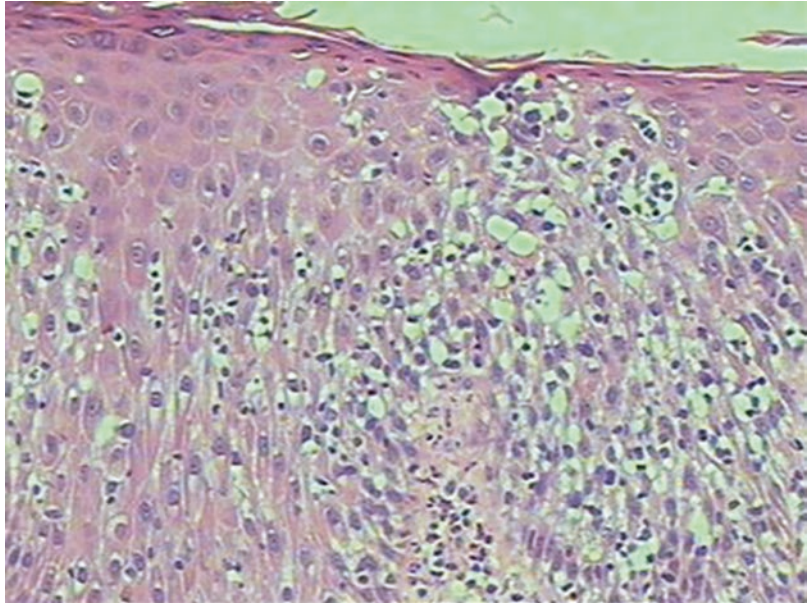
cerebriform nuclei, usually followed by a variable number of eosinophils. The epidermotropism of atypical lymphocytes, with Pautrier's microabscesses, is a histologic mark (Fig. 17.4). However, in the early stages of patches of MF, histologic findings are subtle, with atypias of absent or less prominent lymphocytes, vacuolization with interface changes, and alignment of lymphocytes across the junction. In the early MF, epidermotropism with Pautrier's microabscesses is found in only 19% of the biopsies [16, 19, 29, 32, 40].

With the progression to the tumor stage, the dermal infiltrate becomes diffuse and the epidermotropism may disappear. The tumor cells increase in number and size, presenting variable proportions of small, medium, and large cerebriform cells, and blastic cells with prominent nuclei and intermediate forms [16].

In ichthyosiform MF, a rare variant of MF, although the clinical features are indistinguishable from acquired ichthyosis, the histopathologic findings may be different. These findings reveal epidermotropic infiltrates composed of cerebriform lymphocytes typical of MF [25, 37]. The ichthyosiform area shows compact orthokeratosis and hypogranulosis, characteristic findings of acquired ichthyosis, beyond epidermotropic band-like infiltration, typically MF bands [25].

Granulomatous MF histologically presents with infiltrate similar to sarcoidosis or annular granuloma. Epidermotropism of atypical lymphocytes is present in only half of the cases. The granulomatous MF and granulomatous cutis laxa may overlap and often have identical histologic characteristics, so that a distinction must be based on clinical manifestations with occurrence of voluminous skin folds in the intertriginous areas in the cutis laxa [29].

In folliculotropic MF histology is diagnostic, with minimal epidermal involvement and prominent lymphocytic infiltrate of cerebriform cells inside and around follicles, with variable deposition of mucina, and follicle tropism instead of epidermotropism [16, 17, 19, 34]. Most cases show mucinous degeneration of the hair follicles (follicular mucinosis) upon Alcian blue staining and are traditionally categorized as MF associated with follicular mucinosis [16]. In some cases, prominent infiltration of the follicular epithelium and eccrine sweat glands may be observed [34]. Similar cases with prominent infiltrate of eccrine glands, often associated with alopecia, are called syringotropic MF [41].

In pagetoid reticulosis, histologically there is a hyperplastic epidermis with marked infiltration by isolated pagetoid cells or nests. Atypical cells

have small, medium, or large size and sometimes hyperchromatic and cerebriform nuclei, besides abundant vacuolated cytoplasm. The upper dermis may show lymphocytic or histiocytic infiltrate, but does not present with neoplastic T cells [16, 29].

Immunohistochemistry

MF is a neoplasia that classically presents predominantly the CD4+ phenotype. In addition to CD4, CD2, CD3, CD5, b-F1, and CD45RO are positive (Figs. 17.5 and 17.6). The phenotype CD8 is usually negative. Recently, several other phenotypes

Fig. 17.5 CD45 positive in a patient with mycosis fungoides
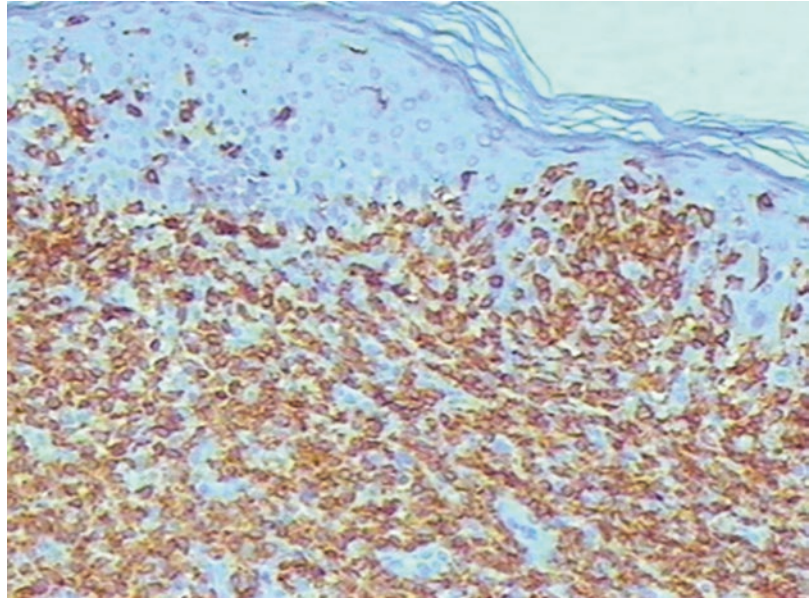
Fig. 17.6 CD3 positive in a patient with mycosis fungoides
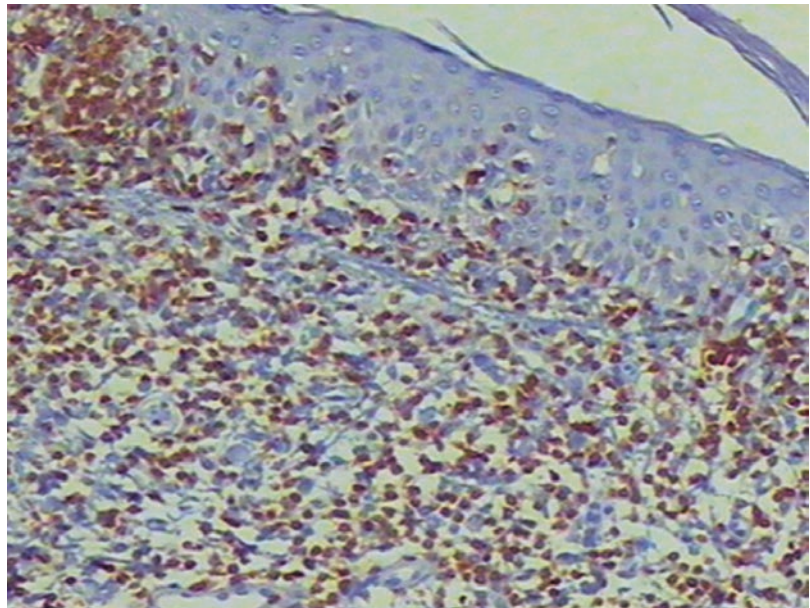
were described, such as CD8+ and CD56+ MF with CD4− and CD8−. The difference in these markers does not seem to influence the prognosis or course of the disease [16, 29, 42]. The CD7 marker is usually deleted in MF [19, 32, 42]. Demonstration of an aberrant phenotype, for example, the loss of pan-T antigens CD2, CD3, and CD5, is frequently observed, and is an important adjunct to diagnosing MF. The expression of cytotoxic proteins (TIA1 and granzyme B) by neoplastic T cells is detected in 10% of MF plaques, but is more frequent in tumors with blastic transformation [16]. Sporadically, reactivity for CD15 is observed in advanced tumor stages of MF. Tumor cells may also show reactivity for CD30 in the stage of plaques and tumors.

Folliculotropic MF has neoplastic cells with phenotypes CD3+, CD4+, and CD8−, in most cases, as well as classic MF [16]. Pagetoid reticulosis is an MF variant with variable phenotypes, including CD3+, CD4+, and CD8− or CD3+, CD4−, and CD8+. The phenotype CD30 is also frequently expressed [16, 29].

Atypical cells of granulomatous cutis laxa express phenotypes CD3+, CD4+, and CD8− [16, 32].

Diagnosis

> Clinical manifestation + histopathologic examination, with immunohistochemistry.

Differential Diagnosis

Fungal infections, eczemas, pityriasis (rosea, lichenoid), psoriasis, leprosy, neoplasias.

Investigation

Lactate dehydrogenase (LDH), hepatic function, total blood cell count (all cases), Sézary cell count or immunophenotyping of blood cells, thorax and abdomen computed tomography (CT), lymph node biopsy (if palpable), bone marrow biopsy (tumoral stages).

Prognosis

For MF, the classification TNM (T, extension of the primary tumor; N, absence or presence and the extension of regional lymph nodes metastasis; M, absence or presence of distant metastasis) is used to estimate prognosis. However, this staging system is primarily used to define the extent of the disease and not as a prognostic guide [3, 43].

The most important predictors of survival in the MF are the T (tumor, in the TNM classification), extracutaneous manifestations, and age of the patient. Other independent factors of adverse prognosis include thickness of tumor infiltration, loss of T-cell markers, such as CD5 and CD7, existence of a T-cell clone in the peripheral blood in any stage of the disease, and chromosomal abnormalities in T cells [32, 44]. Blood involvement considered leukemic, with a large number of tumor cells in the blood, is considered comparable regarding prognosis with nodal involvement [44]. Marked eosinophilia is also a factor associated with worse prognosis [32].

Serum markers, such as lactate dehydrogenase (LDH), β2-microglobulin, and interleukin-2 are associated with a more aggressive disease. Multivariate analyses reveal that Stages IIb (tumors with or without lymph node compromise or metastases) and IV (any cutaneous lesion with metastasis or lymph node compromise) and age older than 60 years are independent predictors of worse survival [44]. Generalized cutaneous involvement is also considered a factor for worse prognosis [43].

Patients with MF in the stage of patches and plaques have life expectancy similar to persons without the disease. In the tumor stage, the 5-year survival rate is 70–80% [16]. Those with erythrodermal MF also generally have a worse prognosis [32].

There are at least two histologic findings that seem to be implicated, as independent factors, in a worse prognosis in MF: folliculotropic involvement (follicular mucinosis) and transformation to large cells [32, 44]. CD30 expression in MF

previously negative is frequently associated with progression to large cell lymphoma and presents a worse prognosis [42].

Moreover, the ulceration which can occur in the plaques and tumors of MF is usually a marker of worse prognosis. However, ulcerations caused by infection or necrosis because of multivariate analyses do not seem to change the prognosis. Studies using multivariate analyses also did not show independent prognostic value of bone marrow involvement [44].

Therapeutic Approach

Treatment of early MF, with skin-confined lesions, uses potent topical corticosteroids, calcineurin inhibitors, topical bexarotene, topical chemotherapy with nitrogen mustard (mechlorethamine or carmustine), phototherapy with ultraviolet B (UVB), narrow-band UVB, psoralens with ultraviolet A (PUVA), or localized irradiation or total skin electron irradiation (electron bath). In the cases with infiltrated plaques and tumors, there is preferential indication for total skin electron irradiation. The biological response modifiers, such as interferon (IFN)-α, bexarotene, and interleukin-2 fused to diphtheria toxin (denileukin diftitox) are increasingly used alone or in combination with topical treatments in advanced skin disease, systemic disease, and refractory cases, with partial remission rates. Polychemotherapy schemes similar to the ones used for non-Hodgkin nodal lymphomas are indicated in the cases of lymph node and/or visceral compromise and "advanced cutaneous disease refractory to the schemes directed to the skin" [3, 17, 19, 28, 32, 45–48].

The treatment for pagetoid reticulosis consists in surgical excision of single lesions or localized radiotherapy [16, 17]. In some cases, topical nitrogen mustard or topical steroids can be acceptable alternatives [16].

The treatment for granulomatous cutis laxa, although the clinical course is indolent, is difficult. Surgical excisions are followed by relapses. Radiotherapy can control the localized disease, but experiments with this method are limited [16, 17]. Other treatment options include radiation, PUVA, IFN, retinoids, and steroids, none of which show strong evidence of efficacy [32].

Sézary Syndrome

Clinical Presentation

SS, occurring exclusively in adults, is historically defined by the triad erythroderma, generalized lymphadenopathy, and presence of neoplastic T cells (Sézary cells) on skin, lymph nodes, and peripheral blood. Erythroderma is intensely itchy and may be associated with severe edema, exfoliation, and lichenification (Figs. 17.7 and 17.8). Moreover, alopecia, palmoplantar hyperkeratosis, and onychodystrophy are frequent clinical findings [16, 17].

Complementary Examinations

The recommended criteria for the diagnosis of SS include the presence of one or more of the following: (i) an absolute Sézary cell count of at least 1,000 cells/mm³; (ii) a CD4/CD8 ratio of 10 or higher caused by an increase in circulating T cells and/or an aberrant loss or expression of pan-T-cell markers by flow cytometry; (iii) increased lymphocyte counts with evidence of a T-cell

Fig. 17.7 Sézary syndrome, Exfoliative erythroderma in face

Fig. 17.8 Sézary syndrome. Exfoliative erythroderma in lower limbs

clone in the blood by the Southern blot or polymerase chain reaction technique; or (iv) a chromosomally abnormal T-cell clone [16, 49].

Histopathologic Examination

It can be similar to that for MF, but specific characteristics, such as epidermotropism of atypical lymphocytes, are found in only 40% of biopsies, and the cell infiltrate is more monotonous [16, 29, 32]. In the other cases infiltrates are found in the band of small lymphocytes, with or without nuclear atypia, and absence of epidermotropism or only a subtle perivascular infiltrate. There is leukemic dissemination of atypical tumor cells with large lymphocytes, called Sézary cells [29, 32].

Immunohistochemistry

SS presents a rise in CD4/CD8 count and aberrant CD3+, CD4+, CD5+, and CD45RO+ rates. CD7, CD8, and CD26 phenotypes are usually negative in circulating Sézary cells, although especially CD7 has been described as positive in some cases. In cases with CD3+, CD4+, and CD8+ predomi-

nantly on the T-cell population in the skin and peripheral blood, actinic reticuloid dermatosis must be considered [16, 19, 31, 32, 44, 47].

Diagnosis

One or more of the following: (i) an absolute Sézary cell count of at least 1,000 cells/mm³; (ii) a CD4/CD8 ratio of 10 or higher caused by an increase in circulating T cells and/or an aberrant loss or expression of pan-T-cell markers by flow cytometry; (iii) increased lymphocyte counts with evidence of a T-cell clone in the blood by the Southern blot or polymerase chain reaction technique; or (iv) a chromosomally abnormal T-cell clone.

Differential Diagnosis

Causes of erythroderma, for example, drug eruption, eczemas, and psoriasis.

Investigation

LDH, hepatic function, total blood cell count (all cases), Sézary cell count or immunophenotyping of blood cell, thorax and abdomen CT, lymph node biopsy (if palpable), bone marrow biopsy.

Prognosis

Unlike MF, SS is an aggressive disease with reserved prognosis, with 5-year survival rates ranging from 10% to 20%. As for MF, the TNM classification can also be used to estimate the prognosis. Other prognostic factors are similar to those of MF, as mentioned above [16, 17].

Absence of markers such as CD5 and CD7 in SS are factors independent of worse prognosis. Presence of CD8+ cytotoxic T lymphocytes infiltrating the dermis is associated with a better prognosis [45].

Therapeutic Approach

Extracorporeal photopheresis, when available, is the therapy of choice, either alone or in combination with other therapeutic modalities, such as IFN-α, with variable response rates. Treatment

with PUVA in association with IFN-α, isolated IFN-α, and combination of chlorambucil and prednisone or methotrexate may be used, but have low complete remission rates [3, 16, 17, 32]. PUVA alone or potent topical corticosteroids may be used as adjunctive therapy. Recent studies show beneficial effects of bexarotene and alemtuzumab (anti-CD52) [3, 16, 50, 51].

Adult T-Cell Leukemia/Lymphoma

Clinical Manifestations and Complementary Examinations

ATLL has, in 100% of the cases, evidence of integration of the virus of the HTLV-1 in the host genome [23–25]. Lymphoma develops in about 5% of seropositive individuals, typically after more than two decades of viral persistence [17].

ATLL appears on the skin in various forms: as erythroderma, infiltrated plaques, papules, nodules, tumors, or patches. Less commonly, the lesions may appear as purpuric plaques or in the form of vesicles. They are always multiple and are generalized in 50% of cases. The tumors and nodules appear in the more aggressive forms (acute, lymphomatous).

ATLL has a broad clinical spectrum divided into four clinically distinct entities (acute, chronic, smoldering, and lymphomatous) that differ in their presentation, progression, and response to treatment. The characteristics of these clinical types are as follows.

Acute ATLL: characterized by fever, cough, lymphadenopathy, skin lesions, hepatosplenomegaly, marked leukocytosis, and hypercalcemia; high serum levels of LDH; atypical lymphocytes with characteristic convoluted or lobulated nuclei and basophilic cytoplasm (flower cells), characteristic of this type of ATLL.

Lymphomatous type: lymph node enlargement with or without extranodal lesions; no lymphocytosis and hypercalcemia; sporadic circulating leukemia cells may be seen (<1%).

Chronic-type: presence of lymphocytosis; LDH value up to twice the normal upper limit; no hypercalcemia; 5% or more of atypical lymphocytes in peripheral blood; no involvement of central nervous system, bone, or gastrointestinal tract; no body effusions.

Smoldering type: few leukemia cells in the peripheral blood (<5%); no lymphocytosis and hypercalcemia; LDH levels either slightly elevated or normal; skin and or pulmonary lesions may be present; no involvement of other organs. The leukemic smoldering type is characterized by the presence of 5% or more atypical cells in peripheral blood [52].

Histopathologic Examination

Biopsy, especially of erythematous areas, may not be specific and also has histologic features indistinguishable from MF, presenting dermal and epidermal infiltration with atypical lymphocytes with polylobulated or pleomorphic nuclei, with or without Pautrier's microabscess [19, 24, 25]. The chronic form may show sparse dermal infiltrate with only slightly atypical cells [16].

Immunohistochemistry

Histology may be indistinguishable from MF, although negative cutaneous lymphocyte antigen (CLA) and the presence of HTLV-1 integrated to the lesions favor lymphoma/leukemia [16, 19]. Neoplastic T cells express phenotypes CD3^{+}, CD4^{+}, CD8−, and CD25^{+} [16].

Diagnosis

Clinical manifestation + histopathologic examination, with immunohistochemistry.

Differential Diagnosis

Fungal infections, eczemas, pityriasis (rosea, lichenoid), psoriasis, leprosy, neoplasias, drug eruption.

Investigation

HTLV serology, LDH, hepatic function, total blood cell count (all cases), Sézary cell count or immunophenotyping of blood cells, thorax and abdomen CT, lymph node biopsy (if palpable), bone marrow biopsy.

Prognosis

In adult T-cell leukemia/lymphoma the prognosis depends on the clinical subtype. The acute and lymphomatous forms present survival rates ranging from 2 months to just over a year. The chronic and smoldering forms present more protracted course and longer survival, with transformation to acute and aggressive course occurring [1, 16, 17, 31].

Therapeutic Approach

In most forms of adult T-cell leukemia/lymphoma, there is the indication for systemic chemotherapy. In chronic forms, skin lesions may be treated with skin-targeted therapies classically used for MF. The combination of IFN-α and PUVA and the use of antiretroviral drugs, such as zidovudine, seem to benefit patients [16, 17, 53, 54].

Primary Cutaneous CD30+ Lymphoproliferative Diseases

Primary Cutaneous Anaplastic Large Cell

Clinical Manifestations

Anaplastic large cell PCL presents with large solitary or grouped tumors, which are frequently ulcerated. It is more common in young adults, with males being two to three times more frequently affected than females. Spontaneous, partial, or complete regression may occur [17].

Complementary Examinations

Histopathologic Examination

Diffuse and dense, nonepidermotropic, large pleomorphic tumor cells, and anaplastic or immunoblastic infiltrate with high mitotic index is found, with possible eosinophils [16, 29]. Reactive lymphocytes are often present on the periphery of the lesions [16].

Immunohistochemistry

By definition, more than 75% of the tumor cells must express the CD30 antigen, hence the name CD30+ large T-cell PCL [16, 29, 42].

Other antigens expressed include CD4, CD25, HLA-DR, CD71, and EMA, although the latter has already been reported as negative in other studies [16, 19, 29, 32, 42, 55]. There is a variable loss of CD2, CD5, CD3, and CD7 and frequently the expression of cytotoxic proteins (granzyme B, TIA-1, and perforins). Less than 10% of the cases have phenotype CD8+ and most express CLA, but do not express ALK [16, 29, 42]. CD56 expression is rare, CD15 is negative [42], and ALK-1+ has been observed more frequently in pediatric cases [56].

Diagnosis

Clinical manifestation + histopathologic examination, with immunohistochemistry.

Differential Diagnosis

Lymphomatoid papulosis, B lymphoma, fungal infections, leprosy, neoplasias.

Investigation

LDH, hepatic function, total blood cell count (all cases), Sézary cell count or immunophenotyping of blood cells, thorax and abdomen CT, lymph node biopsy (if palpable), bone marrow biopsy.

Prognosis

CD30+ T-cell PCL has better prognosis when compared with PCL that do not express CD30+ [55].

Anaplastic large cell PCL is an indolent neoplasia with good prognosis and 10-year survival rate of more than 90%. Cutaneous relapses are frequent and extracutaneous dissemination occurs in about 10% of the cases, mainly to regional lymph nodes. Multifocal skin disease or involvement of regional lymph nodes does not appear to change the prognosis of patients with localized cutaneous lesions [16, 17, 42].

Therapeutic Approach

In anaplastic large cell PCL, radiotherapy or surgical excision is the treatment of choice when the lesions are located. Methotrexate in low doses or radiotherapy may be alternatives for patients with

multiple lesions without curative therapeutic modality. Rapidly progressive or extracutaneous disease must be treated with systemic polychemotherapy using doxorubicin [16, 17, 25, 32, 45, 57].

Lymphomatoid Papulosis

Clinical Manifestations

Lymphomatoid papulosis (LP) is characterized by multiple papulonodular lesions, sometimes papulonecrotic, chronic lesions, tending to spontaneously regress after some weeks or months, and to recur (Fig. 17.9). These can ulcerate and settle with pigmented scars. They predominate on the torso and limbs and usually persist for years or decades. Vesiculopustular lesions may also be seen [16, 29, 42, 58].

LP usually occurs in adults with an average age of 45 years, with a male/female ratio of 1.5:1, and can occur in children. In up to 20% of LP cases this may be preceded, associated with, or followed up by another type of cutaneous malignant lymphoma, usually MF, anaplastic large cell PCL, or Hodgkin lymphoma [16].

Complementary Examinations

Histopathologic Examination
LP exhibits a range from large CD30+ anaplastic or pleomorphic tumor cells, sparse or grouped, followed by neutrophils and eosinophils, with

Fig. 17.9 Lymphomatoid papulosis. Papulonodular lesion

infiltrate similar to Reed-Sternberg cells (type A); epidermotropic infiltrate of small lymphocytes with cerebriform nuclei similar to MF (type B) (Fig. 17.10); or cohesion of CD30+ tumor cells with few mixed reactive cells, similar to large anaplastic cell PCL (type C) [16, 29, 42, 58].

Immunohistochemistry
LP is among the CD30+ lymphoproliferative diseases. The classic type of LP (type A) besides CD30+ has phenotypes CD3+, CD4+, and CD8−. Aberrant phenotypes may occur, with loss of one or more of these antigens. In LP, cells usually express TIA, perforin, and granzyme B [42]. Other phenotypes with CD8+ or CD56+ are also observed. Tumor necrosis factor associated with factor 1 (TRAF-1) and MUM1 are also described as markers for differentiation between LP and PCL with anaplastic large cell, but contradictory results are observed regarding the diagnostic value [29]. One type of LP has lesions with phenotypes CD3+, CD4+, and CD8− and does not express the CD30 antigen [16].

Apoptosis markers such as caspase-3 are increased in the LP when compared with anaplastic large cell PCL, suggesting that apoptosis is a mechanism involved in the spontaneous regression of the LP lesions [16, 19].

Diagnosis

> Clinical manifestation + histopathologic examination, with immunohistochemistry.

Differential Diagnosis
Anaplastic large cell PCL, fungal infections, ecthyma, lichenoid pityriasis, vasculitis, neoplasias.

Investigation
LDH, hepatic function, total blood cell count (all cases), Sézary cell count or immunophenotyping of blood cells, thorax and abdomen CT, lymph node biopsy (if palpable), bone marrow biopsy.

Fig. 17.10 Lymphocytes with enlarged and hyperchromatic nuclei infiltrating the epidermis (epidermotropism) in a patient with lymphomatoid papulosis
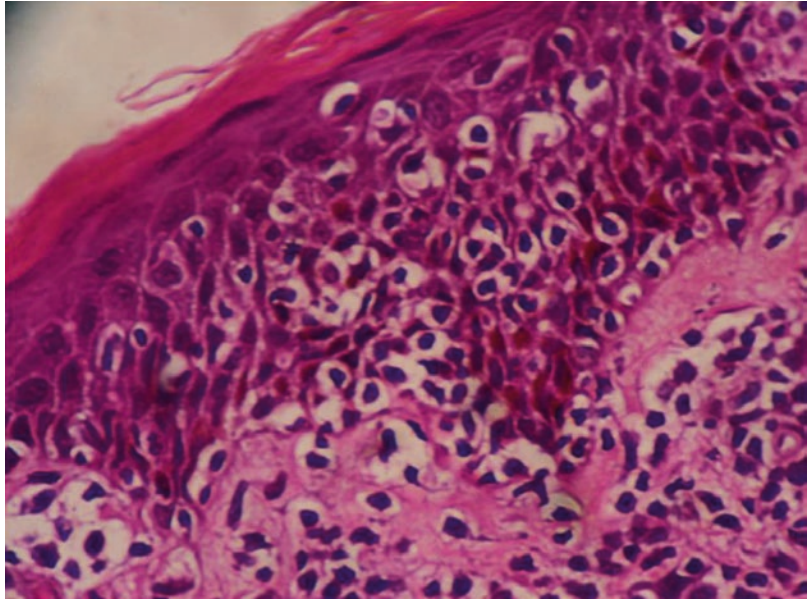
Fig. 17.11 Nodules and ulceration in a patient with subcutaneous panniculitis-like T-cell lymphoma
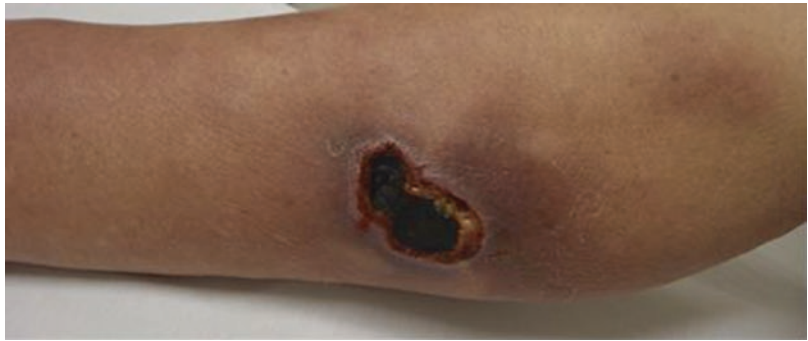
Prognosis

LP has an excellent prognosis, with a survival rate of 100% in 5 years, although 10–20% of the patients can develop a secondary lymphoid neoplasia [16, 17, 45]. Borderline cases between LP and PCL with anaplastic large cell have excellent prognosis, which is similar to that of LP [19].

Therapeutic Approach

There is no curative treatment for LP. Oral methotrexate in low doses (5–20 mg/week) is the most effective therapy to prevent the appearance of new lesions [16, 59]. The use of topical and systemic corticosteroids, PUVA, chemotherapy, or radiotherapy can induce temporary remission. The risk/benefit of these therapies must be carefully evaluated. Periodic clinical follow-up of these patients is recommended [16, 17, 32, 42, 45, 57].

Subcutaneous Panniculitis-Like T-Cell Lymphoma

Clinical Manifestations

This lymphoma is clinically similar to a panniculitis. It manifests with subcutaneous solitary or multiple nodules and plaques, which are occasionally ulcerated, predominantly in the lower limbs of young adults (Fig. 17.11). Constitutional symptoms such as weight loss, fatigue, and low-grade fever may be present [16, 19, 32, 60]. Both sexes are equally affected [16, 60].

The disease can be complicated by a hemophagocytic syndrome, which is generally is associated with a rapidly progressive course [31, 60, 61]. Dissemination to extracutaneous locals is rare and can be preceded by years or decades of a seemingly benign panniculitis [61].

Complementary Examinations

Histopathologic Examination

Histology demonstrates lobular and septal infiltrate of small and medium, and sometimes large lymphoid cells, with pleomorphic nuclei, without dermoepidermal involvement, often with many macrophages. Karyorrhexis, cytophagocytosis, and necrosis may be present. Tumor cells can be surrounded by lymphocytes, but this is not a specific characteristic of the disease since it can be observed in the lupus panniculitis, which is one of its main differential diagnoses [29, 32, 61]. Involvement of individual fatty cells by neoplastic T cells is useful for the diagnosis, although it is also nonspecific. In the first stages neoplastic infiltrates may lack significant atypia, and a dense inflammatory infiltrate may be prevalent [16, 61].

Immunohistochemistry

The panniculitis-like T-cell lymphoma has variable phenotype, usually CD8+, but may be CD4− and CD8− and less commonly CD4+, with variable deletion of CD5 and CD7. It also expresses cytotoxic proteins CD2 and CD3. CD30 and CD56 are rarely expressed [16, 29, 32]. According to the WHO/EORTC, this lymphoma is by definition restricted to cases expressing T-cell receptor (TCR) phenotype α/β. The demonstration of TCR-α/-β expression by immunohistochemistry is the main diagnostic marker of this entity [29]. In panniculitis-like T-cell lymphoma, TIA-1 and granzyme B are also frequently positive in the atypical lymphocytes [19].

Diagnosis

Clinical manifestation + histopathologic examination, with immunohistochemistry.

Differential Diagnosis

Fungal and bacterial infections, vasculitis, panniculitis, neoplasias.

Investigation

LDH, hepatic function, total blood cell count (all cases), Sézary cell count or immunophenotyping of blood cells, thorax and abdomen CT, lymph node biopsy (if palpable), bone marrow biopsy.

Prognosis

In contrast to initial studies indicating a rapidly fatal course in the subcutaneous panniculitis-like T-cell lymphoma, recent studies suggest an usually protracted evolution with recurring subcutaneous lesions, without extracutaneous dissemination and with 5-year survival rate of more than 80% [16, 17]. CD56 expression may be associated with a low survival rate [16, 29, 31, 32].

In contrast to the rapidly fatal course of this disease earlier described, studies have shown that cases with the phenotype CD8+, α/β+ have a longer course, with recurrent subcutaneous lesions and no extracutaneous dissemination [16].

Therapeutic Approach

Treatment for subcutaneous panniculitis-like T-cell lymphoma usually employs polychemotherapy, with doxorubicin and radiotherapy. However, many patients can be controlled with prolonged systemic corticosteroid therapy [16, 17, 32, 42, 60].

Extranodal NK/T-Cell Lymphoma, Nasal Type

Clinical Manifestations

ENKL nasal type occurs in middle-aged to older adult patients, predominantly male, with nodules or solitary or multiple, erythematous red and purpuric tumors, forming extensive necrotic areas, sometimes being ulcerated and rapidly progressive, involving usually the nasal cavity and nasopharynx, but also the torso and extremities. The involvement of the skin may be a primary or secondary manifestation of the disease. Occasionally,

patches and plaques similar to those of MF may be present.

It is known by its strong association with the EBV and was previously called "lethal midline granuloma" when located in the nasal cavity [16, 25, 26]. The main differential diagnosis is the MF tumor stage [56]. Systemic symptoms such as weight loss, indisposition, and fever may be present, and some cases are followed by hemophagocytic syndrome. The disease is closely related to aggressive NK-cell leukemia, which can also present cutaneous manifestations and is also associated with EBV [16].

Complementary Examinations

Histopathologic Examination
Histology shows a cell infiltrate, which is variable (angiocentric and angiodestructive, superficial and deep), composed of histiocytes, plasma cells, and granulocytes, and mainly eosinophils, involving the dermis and frequently subcutaneously, with vascular destruction and sometimes extensive necrosis [17, 19]. It may be similar to the histology of MF, with epidermotropism, although the infiltrate tends to extend deeply [26, 56]. It has a wide cytologic range, from small to large cells, with most cases involving medium-sized cells. Cells may have irregular or oval nuclei, moderately dense chromatin, and pallid cytoplasm. In some cases a dense inflammatory infiltrate of small lymphocytes, histiocytes, plasmatic cells, and eosinophils can be observed [16]. There is usually marked angiotropism or angiodestruction [56].

Immunohistochemistry
Atypical cells of ENKL nasal type usually have immunophenotype with positivity of CD2, DC56, and cytoplasmic proteins (TIA-1, granzyme B, perforin), and negativity of CD3 on the surface (cytoplasmic positivity). In rare CD56− cases, EBV detection by in situ hybridization and the expression of cytotoxic proteins are necessary for diagnosis. CD5 and TCR gene rearrangements are generally negative. Antigen latent membrane protein 1 (LMP-1), related to the EBV, can be expressed in these lymphomas [16, 19].

Diagnosis

> Clinical manifestation + histopathologic examination, with immunohistochemistry.

Differential Diagnosis
Fungal and bacterial infections, syphilis, leishmaniasis, leprosy, vasculitis, neoplasias.

Investigation
LDH, hepatic function, total blood cell count (all cases), Sézary cell count or immunophenotyping of blood cells, cranial, thorax, and abdomen CT, lymph node biopsy (if palpable), bone marrow biopsy.

Prognosis
ENKL nasal type usually has a rapid and aggressive course with a high mortality rate despite treatment. The average survival rates reported are between 5 and 27 months, with the best rates for cases with exclusively cutaneous lesions. The main factor in poor outcome and low survival rate is the presence of extracutaneous involvement at the time of the diagnosis [16, 17].

Some cases of expression of CD30+ and CD56+ have reported a better prognosis and can be large T-cell PCL with co-expression of CD56 [16].

Therapeutic Approach
The treatment indicated is systemic chemotherapy, but the results are disappointing [3, 16, 17]. For patients in the early stage, radiation therapy is the first choice of treatment [3].

Epidermotropic CD8+ Cutaneous T-Cell Lymphoma (Provisional Entity)

Clinical Manifestations
It presents with nodules, tumors, and ulcerated or eroded plaques with central necrosis, and disseminated or localized, rapidly evolving papules [16, 17, 29]. Keratotic plates may occur [16, 17].

This type of lymphoma can disseminate to other sites such as lung, testicle, central nervous system, and oral mucosa; however, nodes are usually spared [16].

Complementary Examinations

Histopathologic Examination
In general, there is an atrophic or acanthotic epidermis, epidermotropic infiltrate of small and medium lymphocytes with pleomorphic nuclei, numerous necrotic keratinocytes, erosion, ulceration, and variable spongiosis. Invasion and destruction of cutaneous appendages are commonly observed, and angiocentricity and angioinvasion can be present [16, 17, 29]. This subtype of PCL must be distinguished from CD8$^+$ MF, which also shows epidermotropic infiltrate in bands, but few or no necrotic keratinocytes. In contrast with PCL of aggressive (epidermotropic) CD8$^+$ cells, CD8$^+$ MF clinically manifests with hyper- or hypopigmented patches and plaques, but not with erosions, necroses, or ulcerations [29].

Immunohistochemistry
The tumor cells of aggressive PCL of epidermotropic CD8$^+$ T cells express phenotype β-F1$^+$, CD3$^+$ CD8$^+$, TIA1$^+$, granzyme B$^+$, perforin$^+$, CD45RA$^+$, CD45RO$^-$, CD2$^-$, CD4$^-$, CD5$^-$, and CD7$^-$, with EBV usually being negative [16, 29].

Diagnosis

> Clinical manifestation + histopathologic examination, with immunohistochemistry.

Differential Diagnosis
Other cutaneous T-cell lymphomas, fungal and bacterial infections, vasculitis, neoplasias.

Investigation
LDH, hepatic function, total blood cell count (all cases), Sézary cell count or immunophenotyping of blood cells, thorax and abdomen CT, lymph node biopsy (if palpable), bone marrow biopsy.

Prognosis
The aggressive epidermotropic CD8$^+$ cutaneous T-cell lymphoma usually has acute evolution with rapid systemic disseminations. The median survival is 32 months [16, 17, 62].

Therapeutic Approach
In the PCL of epidermotropic CD8$^+$ T cells, the treatment of choice is systemic chemotherapy with regimens containing doxorubicin [16, 17].

Cutaneous γδ T-Cell Lymphoma (Provisional Entity)

Clinical Manifestations
It usually presents with disseminated plaques, nodules, or ulcerous and necrotic tumors, particularly in the extremities, although other areas may be affected. The involvement of mucosa is frequently observed, but the involvement of lymph nodes, bone marrow, and spleen is not common. Hemophagocytic syndrome can occur in patients with tumors of the panniculitis type [63].

Complementary Examinations

Histopathologic Examination
Three major histologic patterns may be present in the biopsy: epidermotropic, dermal, and subcutaneous. Often, more than one histologic pattern is present in the same patient in different biopsies or a single biopsy [63]. Neoplastic cells are generally medium to large, with coarse chromatin [16]. Apoptosis and necrosis are common, often with angioinvasion [16, 29].

Immunohistochemistry
The cutaneous γδ T-cell lymphoma has tumor cells that express CD2, CD3, CD56, and cytotoxic proteins, but they are mostly negative for b-F1, CD5, and EBV. Most cases lose CD4 and CD8. CD7 can be positive or negative [16, 29, 33].

Diagnosis

> Clinical manifestation + histopathologic examination, with immunohistochemistry.

Differential Diagnosis

Other cutaneous T-cell lymphomas, fungal and bacterial infections, vasculitis, neoplasias.

Investigation

LDH, hepatic function, total blood cell count (all cases), Sézary cell count or immunophenotyping of blood cells, thorax and abdomen CT, lymph node biopsy (if palpable), bone marrow biopsy.

Prognosis

In cutaneous γδ T-cell lymphoma, most patients have an aggressive chemo- or radiotherapy-resistant disease, with average survival of 15 months [16, 17, 63].

Therapeutic Approach

The treatment of choice is systemic chemotherapy, even though it has produced disappointing results [16, 17].

Cutaneous Lymphoma of Small and Medium Pleomorphic CD4+ T Cell (Provisional Entity)

Clinical Manifestations

It presents, in most cases, with lump, plaque, papule, or solitary erythematous tumor, with no patches and preliminary plates, usually on the face, neck, or upper torso [16, 29, 56, 57]. Less commonly it presents with multiple lesions [57] and, rarely, with ulceration [56].

Complementary Examinations

Histopathologic Examination

Nodular infiltrates of small and medium-sized pleomorphic lymphocytes, eosinophils, erythrocytes, and histiocytes are found in the dermis, with a tendency to infiltrate the subcutaneously. Epidermotropism may be present focally [16, 29]. A small proportion (less than 30%) of large pleomorphic cells may also be present [16].

The distinction with the nodular form of pseudolymphoma T cells is challenging [29]. The prominence of B-cell components is common, sometimes inducing an erroneous diagnosis of cutaneous B-cell lymphoma [56].

Immunohistochemistry

PCL cells of small and medium CD4+ T cells, by definition, express the phenotypes CD3+, CD4+, CD8−, CD30−, CD5+, and CD7+, especially in localized lesions [16, 32, 42, 56]. Sometimes there is loss of pan-T-cell markers, especially in multiple tumor lesions. Cytotoxic proteins are usually not expressed [16, 42].

Diagnosis

Clinical manifestation + histopathologic examination, with immunohistochemistry.

Differential Diagnosis

Other cutaneous T-cell lymphomas, fungal and bacterial infections, vasculitis, neoplasias.

Investigation

LDH, hepatic function, total blood cell count (all cases), Sézary cell count or immunophenotyping of blood cells, thorax and abdomen CT, lymph node biopsy (if palpable), bone marrow biopsy.

Prognosis

Cutaneous lymphoma of small and medium CD4+ T cell has a favorable prognosis, particularly for cases with single or localized lesions. The estimated 5-year survival rate is approximately 60–80% [16, 17].

Therapeutic Approach

For localized lesions of cutaneous lymphoma of small and medium pleomorphic CD4+ T cell, surgical excision or radiotherapy is recommended [16, 17, 32]. Cyclosporine or IFN-α can be effective in generalized disease. However, the best treatment for these patients is yet to be defined [16, 32].

Glossary

Angiocentric Arrangement of cells around the vessels; perivascular.

Epidermotropism Movement toward the epidermis, as in the migration of T lymphocytes into the epidermis in mycosis fungoides.

Immunohistochemistry A process of detecting antigens (e.g., proteins) in cells of a tissue section by exploiting the principle of antibodies binding specifically to antigens in biological tissues

Immunophenotyping A process used to identify cells, based on the types of antigens or markers on the surface of the cell. This process is used to diagnose specific types of leukemia and lymphoma by comparing the cancer cells with normal cells of the immune system.

Pautrier's microabscess A well-defined collection of cells within the epidermis in T-cell lymphoma and mycosis fungoides.

Reed–Stenberg cell A giant binucleated or multinucleated macrophage, characteristic of Hodgkin's disease.

Sézary cell An atypical mononuclear cell seen in the peripheral blood in Sézary syndrome; has a large, convoluted nucleus and scant cytoplasm containing vacuoles that test positive with the periodic acid-Schiff stain.

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Part IV

Dermatologic Diseases in Public Health: Inflammatory and Autoimmune Diseases

Eczemas

18

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Key Points

- Eczemas are one of the most often seen forms of skin diseases and can be classified as acute, subacute, and chronic
- Eczemas can be classified according to clinical and etiopathogenic criteria: eczema or contact dermatitis, eczema or atopic dermatitis, nummular eczema, stasis dermatitis, and dyshidrotic eczema
- There are four different types of eczema or contact dermatitis according pathogenic aspects: irritant contact dermatitis, phototoxic contact dermatitis, allergic contact dermatitis, and photoallergic contact dermatitis

- Atopic dermatitis (AD) is an inflammatory skin disease, often related to asthma or allergic rhinitis
- AD results from the complex relationship involving genetic, immune, environmental, psychosomatic, and pharmacologic factors, and changes in the skin structure
- The two main AD disorders are dysfunctional skin barrier and immunologic reaction, both interrelated.
- In nummular dermatitis the dry skin may be a significant predisposing factor, mainly among older individuals
- Stasis dermatitis or eczema is a chronic condition often seen on the lower limbs, resulting from venous stasis. Multiple factors are important for its etiopathogenesis: lower limb varices, obesity, congenital skeletal and muscular alterations, lower limbs fractures, and planovalgus feet.
- Dyshidrosis can be classified as idiopathic or true, and also as dyshidrosiform eruption if associated with other dermatoses (contact dermatitis, AD, drug eruption, or irritant dermatitis)

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Introduction

Eczemas, or eczematous eruptions, are part of a group of dermatoses characterized by the presence of erythema, edema, infiltration, vesicles, oozing, crusting, flaking, and lichenification. Such changes can occur concomitantly or alternatively according to different evolutionary phases. The word *eczema* comes from the Greek word *eczein* (*ek* – outside, and *zein* – boil), thus characterizing the most usual symptom of dermatosis, pruritus.

Eczemas can be classified as acute, sub-acute, and chronic, depending on their clinical presentation. The acute form shows erythema, edema, vesicles, and oozing. The subacute form of the condition is apparent when the edema and the erythema are less evident and oozing and crust development are prevalent. The chronic forms are characterized by the presence of lichenification.

Eczema is one of the most often seen forms of skin disease resulting from exogenous or endogenous agents, which operate by different pathogenic mechanisms despite showing certain similar clinical aspects.

Eczemas can be classified according to clinical and etiopathogenic criteria, such as:
1. Eczema or contact dermatitis
2. Eczema or atopic dermatitis
3. Nummular eczema
4. Eczema or stasis dermatitis
5. Dyshidrotic eczema

Contact Dermatitis

Contact dermatitis is a kind of eczema caused by exogenous agents in contact with the skin.

There are four different types according to pathogenic aspects:
(a) Irritant contact dermatitis
(b) Phototoxic contact dermatitis
(c) Allergic contact dermatitis
(d) Photoallergic contact dermatitis

Irritant Contact Dermatitis

Introduction

Irritant contact dermatitis (ICD) is an inflammatory skin response to contact with a wide range of possible chemical or physical irritants. It arises as a result of activated innate immunity to direct injury to the skin without prior sensitization [1, 2].

ICD is the most common type of contact dermatitis, representing approximately 80% of occupational contact dermatitis cases. The risk is higher in occupations that involve repeated hand washing or repeated exposure of the skin to water, food, and other irritants, such as cleaning, healthcare, food preparation, and hairdressing [3, 4].

The estimated annual cost of occupational contact dermatitis in the United States exceeds \$1 billion, including medical expenses, workers' compensation, and lost work time. It is therefore a major public health problem. Box 18.1 summarizes the main concepts of the disease [5].

Predisposing Factors

ICD is a multifactorial disorder influenced by both endogenous and exogenous factors. The predisposing host-related susceptibility factors include age (skin reactivity to irritants tends to decrease with age); sex (it occurs more frequently in women); body site (face, dorsum of the hands, and finger webs are more prone to chemical irritants); atopy (individuals with atopic dermatitis have increased susceptibility to irritants as a result of an impaired barrier function); and genetic factors (as shown by twin studies) [1, 5].

The most important predisposing exogenous factors are properties of the irritating substance (molecular size, liposolubility, concentration); and environmental conditions, such as temperature, airflow, humidity, and occlusion (higher temperatures and occlusion increase sweating that may cause disruption of the skin barrier and enhance the inflammatory response to chemical or mechanical irritants; on the other hand, cold temperatures and low ambient humidity increase transepidermal water loss and subsequently skin susceptibility to irritants) [1, 2].

Etiopathogenesis

Unlike allergic contact dermatitis, the immunological reaction in ICD does not require previous sensitization, immunologic memory, or presence of antigens in order to activate lymphocytes [2].

The pathophysiologic mechanisms involved in ICD are complex and can be summarized in the following events: disruption of the epidermal barrier, cytokine release from keratinocytes, and activation of innate immunity [6].

Integrity of the epidermal barrier function plays an important role in the interaction and the response of the human skin to irritants; the disruption (by chemical or physical irritants) results in increased skin permeability and transepidermal water loss (TEWL), which is considered the initiating event of ICD [6, 7].

The disruption of the skin barrier leads to release of preformed interleukin (IL)-1α by keratinocytes, which represents an initial step in the inflammatory cascade of ICD. The primary cytokines involved are IL-1 and tumor necrosis factor α (TNF-α). The synergistic effects of these two cytokines result in the further activation and release of secondary cytokines such as IL-2, IL-6, granulocyte macrophage colony-stimulating factor, interferon (IFN)-γ, vascular endothelial growth factor (VGEF), CXCL8, CCL2, CCL5, and CCL20 by keratinocytes, fibroblasts, and endothelial cells; upregulation of adhesion molecules on endothelial cells; and the subsequent recruitment of leukocytes, thereby perpetuating ongoing inflammation [6].

Common Irritants

Irritants are capable of producing cellular perturbation if applied to the skin for a sufficient time and in sufficient concentration [8]. A primary irritant can cause injury on any skin if exposure takes place. These substances are classified as absolute and relative primary irritants.

Absolute primary irritants cause a strong reaction (chemical burn or severe irritation) on almost anyone's skin. Acids and alkalis are some examples. Cutaneous lesions are acute, appearing rapidly after contact. They are usually associated with accidental exposure [2, 5].

Some absolute primary irritants may cause a delayed response, after 12–24 h of contact with the skin, such as podophyllin and anthralin [2, 5].

Substances with a weak capacity to irritate are classified as relative primary irritants; these are the most common irritants. The dermatitis results from repeated exposures, and in these cases appear in a chronic form. Common relative irritants include water, detergents and surfactants, solvents, food, urine, and feces [2, 5]. Physical irritants include metal, wood, fiberglass, and paper, among others.

Clinical Presentation

The reaction is generally limited to the site of contact, and typically presents as eczema in acute or chronic form. Clinical manifestations may vary according to the type of inflammatory response as well as the kind of irritant and exposure.

Acute ICD often results from a single exposure to an absolute primary irritant. Clinical features usually include erythema, edema, vesicles, bullae, and oozing. In cases of contact with strong irritants, necrosis and ulceration may appear (chemical burn). Patients sometimes report a sensation of burning, stinging, or pain [1, 2, 5].

On the other hand, chronic ICD results from repeated exposures to mild irritants (relative primary irritants), such as soaps and detergents. ICD is characterized clinically by erythema, scaling, lichenification, hyperkeratosis, and fissures [1, 2, 5].

Specific Clinical Examples

Irritant Contact Diaper Dermatitis

Irritant contact diaper dermatitis affects up to 25% of infants wearing diapers, and is the most common cause of diaper dermatitis. It is triggered mainly by prolonged contact between the skin and urine and feces, but other irritants, such as soaps, may contribute. Occlusion raises the local pH and exposure to fecal enzymes damages the integrity of the skin barrier, increasing the susceptibility to irritant and microbial invasion [9, 10].

Clinically, irritant contact diaper dermatitis is most prominent in areas where the diaper is in direct contact with the skin, particularly on the convex surfaces, typically sparing the inguinal creases and gluteal cleft. Clinical manifestations are variable and include redness, papules, scaling, maceration, superficial erosions, and, less commonly, ulceration or elevated papules/pseudoverrucous nodules [9, 10] (Fig. 18.1).

Prevention is key in the management of irritant contact diaper dermatitis. Frequent diaper changes are important for minimizing skin exposure to urine and feces and keeping the infant dry. It is recommended that newborns be changed hourly and older children every 3–4 h. Recent studies have shown that superabsorbent disposable diapers cause less erythema than cloth diapers when changed at appropriate intervals [9–12].

Fig. 18.1 Irritant contact diaper dermatitis

Irritant Contact Hand Dermatitis

Hand eczema is a common condition seen in dermatologic practice, affecting up to 10% of the population, with a negative impact on quality of life. ICD is the main cause (approximately 80% of all cases), frequently aggravated by work (occupational dermatitis) [13, 14].

Irritant contact hand dermatitis is particularly common in people with jobs that involve repeated hand washing (wet work), such as cleaning, catering, hairdressing, healthcare, and mechanical work. Wet work can be defined as activities for which workers have to immerse their hands in liquids for >2 h per shift, or wear waterproof (occlusive) gloves for a corresponding amount of time, or wash their hands >20 times per shift. The most common irritants include water, detergents, solvents, acids, alkalis, cold, heat, and friction [15, 16].

Clinically it is usually a chronic eczema, with erythema, scaling, lichenification, and fissures. Sites commonly affected are fingertips and the dorsum of the hands, usually sparing the palms [13, 14] (Fig. 18.2).

Hand dermatitis may be associated with more than one concomitant kind of dermatitis, so patch testing is always recommended in chronic cases to exclude allergic sensitization.

Management is not always easy as it involves not only symptomatic treatment but also changes in habits and daily work routine.

Therapeutic Approach

The management of ICD includes avoidance of the culprit irritant, treatment of skin inflammation, restoration of the epidermal barrier function, and prevention of further exposure.

After identification of the irritant, alternatives should be given for avoiding direct contact with the substance, such as replacement of products, use of barrier creams, and use of personal protective equipment such as suits, face masks, and goggles.

The occupational physician, who would assist in adapting the work routine, sometimes should also follow occupational irritant contact dermatitis cases.

Emollients are used to decrease irritation, improve or restore the skin barrier function in ICD, and prevent new exposure. Petrolatum-based

Fig. 18.2 Irritant contact hand dermatitis

products are preferred to emollients containing lanolin or fragrances to reduce the risk of contact sensitization [5].

Treatment of cutaneous lesions includes the use of topical corticosteroids for 2–4 weeks. While for severe and chronic cases with lichenification high-potency topical corticosteroids are recommended, for milder forms and sensitive areas (such as face or flexure), medium- or low-potency topical corticosteroids are suggested. Calcineurin inhibitors (pimecrolimus or tacrolimus) may be used in the maintenance phase [5].

Phototherapy is a reasonable option for patients with refractory symptoms.

For severe chronic irritant contact hand dermatitis with conspicuous skin thickening (lichenification), the use of systemic retinoids (acitretin and alitretinoin) or immunomodulators (such as methotrexate and cyclosporine) must be considered [5, 17, 18].

The prognosis of acute ICD is usually good if the offending irritant is removed and preventive measures are adopted. However, for chronic cases the evolution is variable, and the recovery of the barrier function in affected areas may persist for 10 weeks. Negative prognostic factors include history of atopy, disease duration, female gender, and association with allergic contact dermatitis [5, 19].

Detailed orientations regarding avoidance of the irritant and prevention measures are essential for the success of treatment, as it usually depends on behavior changes.

Phototoxic Contact Dermatitis

Phototoxic dermatitis is an inflammatory reaction that occurs when the irritant is activated by sunlight. It has a mechanism similar to that of ICD. The interaction between ultraviolet (UV) radiation (absorbed by chromophores) and the photosensitive substance produce free radicals that cause cytotoxic damage [2, 20, 21].

Some of the main substances that may cause phototoxic contact dermatitis are topical nonsteroidal anti-inflammatory drugs, psoralens, promethazine, sulfadiazine, sulfacetamide, and perfumes (especially those containing oil of bergamot, causing berloque dermatitis).

Clinical presentation is similar to sunburn, with erythema, edema, and sometimes vesicles and bullae restricted to sun-exposed areas (Fig. 18.3).

Phytophotodermatitis is a subtype of phototoxic contact dermatitis caused by plants, vegetables, or fruits containing furocoumarins, such as

Fig. 18.3 Phototoxic dermatitis
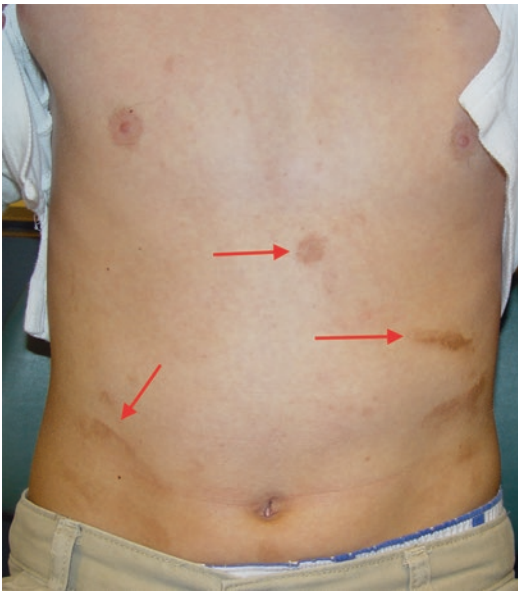
Fig. 18.4 Hyperpigmentation after acute dermatitis

lemons and oranges, activated by UVA radiation. The most common presentation is linear streaks of pruritic dermatitis on a sun-exposed area. After the acute phase heals, marked hyperpigmentation usually develops [20, 21] (Fig. 18.4).

Allergic Contact Dermatitis

Introduction

Sensitizing contact dermatitis or allergic contact dermatitis (ACD) is a type IV or cell-mediated immune reaction according to the Gell and Coombs classification, whereby the subject reacts to certain substances to which he/she has been previously sensitized [22 23]. It is a latent condition that can persist throughout life, and every exposure to a sufficient amount of allergen manifests as eczema [24].

The patch test remains the gold standard in the diagnosis of ACD, although it is still underutilized worldwide [25].

Studying ACD is an exciting work that involves investigative skills to interpret the patch test, relating it to the clinical picture and the activities or occupations of the patient. Educating the patient with ACD is an art and a key to the resolution of the disease. Box 18.2 summarizes the main concepts of disease.

> **Box 18.2 Concepts of Allergic Contact Dermatitis**
> 1. Allergic contact dermatitis is an immune reaction type IV according to Gell and Coombs in an individual previously sensitized
> 2. Itching is a constant symptom
> 3. The patch test remains the gold standard in the diagnosis of ACD, although it is still underutilized
> 4. Nickel remains the most common allergen, followed by fragrances and preservatives
> 5. The main therapeutic measure is the removal of the contact

Epidemiology

In 2010, Lopes et al. reported that eczema generally accounted for 14.6% of the dermatologic consultations in a Brazilian public clinic [26]. Duarte et al. reported a frequency of 5.1% of ACD among patients treated for 10 years at a private practice in Brazil [27].

In 2006, a study was conducted by the Brazilian Society of Dermatology with 932 dermatologists and 49 hospitals that offer residency program, which included 57,000 consultations a week. In this study, 3.9% of consultations were due to contact dermatitis [28]. Although there were no concrete and systematized data in Brazil,

both ICD and ACD are important causes of dermatologic consultations. They even hinder patients from performing their usual activities, causing a great impact on patients' occupation and quality of life [28, 29].

ACD may occur in any age or sex [25, 30]. The frequency of allergen varies with the population and geographic region under study. However, nickel remains the most common allergen in several series [31–35], particularly among children [30, 36] and the elderly [37]. The next most common allergens are fragrances and preservatives [38]. Allergens vary according to periods of time during which certain epidemics are reported: currently the ACD epidemic related to methylisothiazolinone [31–36], which was the 2013 American Contact Dermatitis Society allergen of the year [39–45].

Etiopathogenesis

The mechanisms underlying this chemical-triggered delayed hypersensitivity reaction are not yet fully understood. In recent years, basic research demonstrated that the immune system reacts to combat allergens by activating signaling pathways that are normally used to combat infections [38].

Allergens are substances with physicochemical characteristics such as low molecular weight (less than 500 Da) and low affinity and solubility in lipids, the so-called haptens. These features allow them to cross the skin barrier and stimulate the immune system in susceptible individuals, sensitizing them [23, 46, 47]. The haptens form covalent bonds with the skin proteins, forming the antigen, and this conjugate binds to glycoproteins of the plasma membrane of antigen-presenting cells, such as Langerhans cells (LCs) or dendritic cells [46]. These cells act to internalize, process, and transport the antigens bound to the major histocompatibility complex (MHC) and present them to T lymphocytes from regional lymph nodes through afferent lymphatics. It thus produces the sensitization process [48], and the lack of integrity of the epidermal barrier appears to be the first step in its triggering [48, 49]. Activation and induction of migration of LCs seem to depend on the capacity of haptens to induce the secretion of IL-1β in LCs. IL-1β induction of an event is connected to the hapten contact with the skin and does not occur with irritant substances [25]. Other cytokines, such as TNF-α, may contribute to the activation of LCs.

Haptens can be classified as classic, pro-haptens, and transition metals. The classic haptens follow the path described above. The pro-haptens (for example, urushiol and drugs) need to undergo transformation to become active. Some authors classify haptens based on the type of transformation required: pro-haptens when the process is enzymatic, and pre-haptens when the transformation occurs by environmental action, such as light or oxygen. Since transition metals, such as nickel, chromium, and cobalt, unlike classic haptens, form ionic bonds with their carriers, this class of haptens is considered weaker and less stable [47].

The induction phase, also called the elicitation phase or afferent pathway of ACD, includes the events described from initial contact, often repeated, with the allergen, and ends when the individual is sensitized and able to respond positively to a new contact. For the sensitization to occur, the hapten must remain on the skin for 18–24 h. The least time required to complete the afferent pathway ACD is 4–5 days, and 14–21 days are required for the effector cells to recirculate on the skin [46].

The second step is the ACD elicitation or efferent phase. The elicitation phase starts after re-exposure to the allergen and results in clinical manifestations of ACD.

The antigen recognition is given by the T-cell antigen-specific memory heading toward the site of skin contact and within 24–48 h, the inflammatory reaction develops [46].

At this stage, the main cytokines are IL-1, IL-2, IL-3, IL-6, IFN-γ, and TNF-α [46].

More than 3,700 allergens have been reported as a cause of ACD in humans [50].

Cross-Reactions

It is common for the allergens to initiate cross-reactions with each other, which have important clinical implications.

Strictly speaking, the cross-reactivity occurs when an individual, who was initially sensitized

to a substance, reacts to a second allergen with which he/she never had contact [51]. However, the term cross-reaction is widely used by dermatologists to report simultaneous reactions to two or more substances indiscriminately.

According to Johansen et al., the basis of cross-reactions lies in the fact that two substances of different structures, but with similarity in chemical reactivity and molecular shape, can activate the same T-cell receptors. This could be interpreted as follows: X and Y substances are chemically and structurally similar; X is metabolized similarly to a Y component, or vice versa; or X and Y are both metabolized by similar components. It is often extremely difficult to differentiate between co-reactions or concomitant reactions (simultaneous reactions that occur with substances that are absolutely unrelated) and true cross-reactions mainly because the metabolites are structurally very different from the initial substances and it is very difficult to know what the primary sensitizing agent is: the multiplicity of substances with which humans have contact [49].

Clinical Presentation

ACD typically presents as a well-demarcated, itchy rash usually confined to the site of contact with the allergen. However, there may be diffuse or widespread distribution, depending on the nature of the causal agent [25].

It can be classified as acute, when there is predominant erythema, edema, and vesiculation; subacute, when the edema and erythema are less intense and dominant with demonstrations of secretions with crusting; and chronic, when there is prolonged evolution, with lichenification, variable hyperkeratosis, and cracks [25, 50, 52]. Itching is the constant symptom [52].

As with exogenous eczema, the main locations correspond to parts of the body with greater exposure to the environment: hands, face, neck, feet, and torso. The region involved corresponds to the principal location of contact exposure, especially at the early stage when limited to the contact area of the allergen, which may suggest the source of the substance [50, 52]. With the evolution of the process there may be involvement of other areas, especially in cases of long-term or untimely treatment [52]. Erythrodermia can occur in some cases [53]. It is not uncommon for secondary infection plus regional lymphadenopathy to complicate the picture [52, 53].

With the wide range of possible allergens, the clinical presentation can also vary greatly [50]. The more ubiquitous is the allergen, the more difficult the clinical correlation with exposure, e.g., balsam of Peru (*Myroxylon pereirae*), metals, formaldehyde, and rubber [50] (Fig. 18.5).

The face and eyelids are exposed to a large number of allergens, such as rubber additives (i.e., makeup sponges and toothbrushes), toiletries, cosmetics (i.e., preservatives and fragrances), and metals, which in addition to the direct contact can be easily carried by hand without any injury to these (ectopic contact dermatitis) [50] (Fig. 18.6).

Fig. 18.5 Allergic contact dermatitis
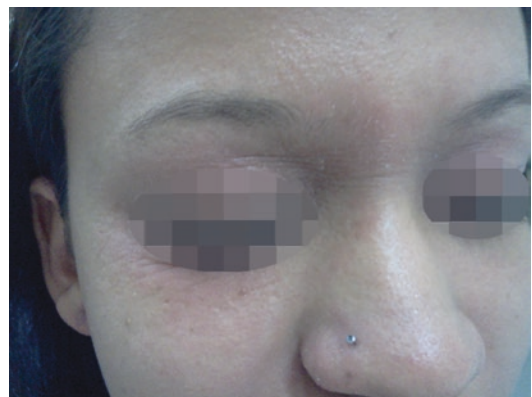
Fig. 18.6 Ectopic contact dermatitis

Scalp ACD has lower sensitivity, possibly due to the greater thickness of the region, changes because of the follicular units, changes in vascularization, and the dilution effect of perspiration [50]. Thus, allergens applied there, such as paraphenylenediamine of hair dyes, fragrances, preservatives, and surfactants of shampoos and conditioners, can cause eczema in adjacent areas, such as the deployment of the hair, eyelids, and retroauricular regions, without causing lesions on the scalp.

In the armpit the major allergens are fragrances, in particular Lyral® [50, 54], but preservatives also have a prominent place. It is common for injuries to spare the axillae, diluting the allergen in perspiration. In the case of aeroallergens, satellite papules may occur due to spreadability [50].

The neck also presents great exposure to environmental allergens and indirect exposure by hands. Frequently, metals and fragrances can lead to the development of Berloque (which comes from a French word that refers to pendant-like pigmentation) dermatitis [50, 52].

Hands are our greatest source of contact with the environment and the pathogenesis is primarily occupational, as can be seen in the case of construction workers, in whom the main allergens are potassium dichromate [55] in cement, and rubber or leather gloves [56]. In the case of hairdressers, paraphenylenediamine, cocamidopropyl betaine, and glycerol monothioglycolate are possible sources [23, 50]. In the literature the major allergens of the hands are metals, fragrances, *Myroxylon pereirae,* and rosin. The latter three are primarily related to soaps, detergents, and cleaning products [24, 57] (Fig. 18.7).

The dorsum of the feet is the preferred location of involvement of ACD and the main allergens refer to footwear, such as rubber, adhesives, and leather [23, 50, 52, 55].

In chronic long-lasting or recurrent cases of ACD the patients can develop sensitivity to multiple agents. The vicious circle of self-eczematization can also occur through scratching-lichenification-scratching, so even when the causative agent is removed the disease persists [52].

Fig. 18.7 Hairdressers: occupational allergic contact dermatitis

Systemic contact dermatitis usually occurs in sensitized individuals in whom topical drugs are given systemically (either orally or parenterally) [50]. A common example is promethazine.

Recall reaction: eczema on sensitization site after systemic exposure (oral, parenteral, or inhalation) [50, 53]. Prolonged exposure can lead to erythroderma. Box 18.3 shows noneczematous variants of ACD.

Box 18.3 Noneczematous Variants of ACD

Contact leukoderma: postinflammatory hypopigmentation or direct chemical toxicity (hydroquinone and rubber) [29, 52].

Contact hyperchromia: mainly caused by fragrances, [52] bleaching clothes, and textile dyes.

Pigmented purpuric eruption: caused by rubber oxidizing agents, cobalt, wool, and some medications (quinidine) [52].

Erythema multiform-like eruption: usually triggered by contact with plants, topical medications, woods, formaldehyde and resin-epoxy, metals, pesticides, and soap [23, 50, 52, 58, 59].

Lichenoid eruption: caused by metals such as nickel and copper, paraphenylenediamine, photographic developers, and resin-epoxy [23, 52].

Granulomatous dermatitis: caused by metals such as mercury, chromium, gold, cobalt, palladium, wool, zirconium, and beryllium [23, 50, 59].

Acneiform contact dermatitis: caused by cosmetics, medicines, oil and oil products, and coal tar [58, 59].

Pustular contact dermatitis: rare; caused by contact with some topical medications and metals, causing follicular obstruction [23, 58].

Contact urticaria: there are two mechanisms:

(a) Immune contact urticaria: immunoglobulin E (IgE)-mediated reaction is the least common form of ACD that occurs mainly by contact with proteins, such as latex [23, 50]. Other causes are foods (eggs, milk, potatoes, meat, seafood, and fruits), medicines, and preservatives.

(b) Nonimmunological contact urticaria: results from the release of vasoactive substances (such as histamine and bradykinin) directly by contact with the substance. It does not require prior sensitization. Examples of substances are preservatives (sorbic and benzoic acids), fragrances (cinnamic acid, cinnamic aldehyde, and *Myroxylon pereirae*), and dimethyl-sulfoxide (DMSO).

Diagnosis

Clinical history should include the onset of lesions, number of episodes, evolution, occupational history, hobbies and leisure activities. The physical examination should pay attention to the description and location of the lesions. Box 18.4 defines the ACD diagnosis.

Box 18.4 Allergic Contact Dermatitis: Diagnosis

Diagnosis is mainly clinical, based on a good anamnesia and location of the lesions, which can be complemented by histopathology and patch test.

Complementary Tests

Patch Test

The gold standard in the diagnosis of ACD is the patch test [48, 52, 60]. Assuming that the patient had prior contact with it, placing the suspected allergen on a body part, typically the torso, will induce the formation of eczematous lesions at the site of application after a standard period. The elucidation of exposure to the allergen source is the core process for establishing the clinical relevance of patch testing and the diagnosis of ACD [32, 61]. Although many allergens are common in different parts of the world, the applied allergens series are variable among them. For example, Europe (European Society on Contact Dermatitis, ESCD) and North America (North American Contact Dermatitis Research Group, NACDRG) have basic series and a variable range of complementary ones. In Brazil, the Brazilian standard patch test series and the cosmetic series [46, 48, 62] are used, composed of 30 and 10 substances, respectively (Tables 18.1 and 18.2).

The test is applied to the patient's back, left for 48 h, then removed so the first reading from the test can be taken. Between 72 and 96 h a second reading should be performed, from which the final test result is provided. The result follows the criteria of the International Contact Dermatitis Group (Table 18.3; Figs. 18.8, 18.9, and 18.10).

A positive patch test does not necessarily mean that the allergen in question is the cause of eczema. It is necessary to correlate the test and the clinical history, at which time the relevance of the test will be established. The relevance can be current or past and the substance may be causing or aggravating the clinical framework [52].

The relevance of the test may be possible, probable, or definite. Possible relevance occurs when there is a possibility of the presence of the allergen in the patient's environment. Probable relevance occurs when the allergen is present in the patient's environment. Definite relevance occurs when there is worsening with the use of the product or the patch test carried out with the product is positive.

Table 18.1 Brazilian standard patch test series

#	Substance	Concentration	Vehicle
1	Anthraquinone	2%	Petrolatum
2	*Myroxylon pereirae*	25%	Petrolatum
3	PPD (mix)[1]	0,4%	Petrolatum
4	Hydroquinone	1%	Petrolatum
5	Potassium dichromate	0.5%	Petrolatum
6	Propylene glycol	10%	Petrolatum
7	Butyl phenol-*p*-tertiary	1%	Petrolatum
8	Neomycin	20%	Petrolatum
9	Irgasan (triclosan)	1%	Petrolatum
10	Kathon CG[2]	0.5%	Petrolatum
11	Cobalt chloride	1%	Petrolatum
12	Lanolin	30%	Petrolatum
13	Thiuram (mix)[3]	1%	Petrolatum
14	Ethylenediamine	1%	Petrolatum
15	Perfume or Fragrance mix I:[4]	7%	Petrolatum
16	Mercapto (mix):[5]	2%	Petrolatum
17	Benzocaine	5%	Petrolatum
18	Quaternium 15	0.5%	Petrolatum
19	Quinoline (mix):[6]	6%	Petrolatum
20	Nitrofurazone	1%	Petrolatum
21	Paraben (mix):[7]	15%	Petrolatum
22	Epoxy resin	1%	Petrolatum
23	Thiomerosal	0.05%	Petrolatum
24	Turpentine	10%	Petrolatum
25	Carba (mix):[8]	3%	Petrolatum
26	Promethazine	1%	Petrolatum
27	Nickel sulfate	5%	Petrolatum
28	Rosin	20%	Petrolatum
29	Paraphenylenediamine	1.0%	Petrolatum
30	Formaldehyde	1%	Water

[1]N-isopropyl, N-phenyl, paraphenylenediamine N,N-diphenyl paraphenylenediamine (0,2% each)

[2]Methylchloroisothiazolinone /methylisothiazolinone (0,5% each)

[3]Tetramethylthiuram monosulfide Tetramethylthiuram disulfide (0,25% each)

[4]Cinnamic alcohol ; α-Amyl cinnamic aldehyde; Cinnamic aldehyde; Eugenol; Isoeugenol; Geraniol; Hydroxycitronella; Oak moss absolute; Sesquioleate sorbitan (1% each)

[5]Mercaptobenzothiazole (2%) ; N-cyclo hexylbenzothiazole sulfonamide; Dibenzothiazyl disulfide ; Morpholinyl mercaptobenzothiazole (1% each)

[6]Clioquinol; Chlorquinaldol (3% each)

[7]Methyl paraben; Ethyl paraben; Propyl paraben; Butyl paraben; Benzyl paraben (3% each)

[8]Diphenylguanidine; Zinc dimethyldithiocarbamate; Zinc diethyldithiocarbamate (1% each)

Table 18.2 Brazilian cosmetics patch test series

#	Substance	Concentration	Vehicle
C1	Germall 115 (imidazolidinyl urea)	2%	Petrolatum
C2	BHT	2%	Petrolatum
C3	Tosilamide formadehyde - resin	10%	Petrolatum
C4	Triethanolamine	2.5%	Petrolatum
C5	Bronopol (2-bromo-nitropropane-1,3-diol 2)	0.5%	Petrolatum
C6	Chloracetamide	0.2%	Petrolatum
C7	Sorbic acid	2%	Petrolatum
C8	Ammonium thioglycolate	2.5%	Petrolatum
C9	Amerchol L-101	100%	–
C10	Chlorhexidine	0.5%	Water

Table 18.3 International system for reading test

Doubtful (?): erythema
+: Erythema, papules, and infiltration
++: Vesicular reaction, with erythema, infiltration, and papules
+++: Confluent bubbles

Fig. 18.9 ++ Reaction

Fig. 18.8 + Reaction

Fig. 18.10 +++ Reaction

Histopathology

Histopathologic examination generally reveals spongiosis, superficial perivascular inflammatory lymphocytic infiltrate in the acute stage, eosinophils that can be observed in the infiltrated areas as spongiosis, and intraepidermal edema, developing into vesicles. In the chronic phase, hyperkeratosis, acanthosis, parakeratosis and hypergranulosis, and fibrosis in the dermal papillae can be seen [52].

Differential Diagnosis

The differential diagnosis includes all forms of eczema: dermatitis and irritant contact, atopic, stasis, and xerotic eczema, and seborrheic dermatitis.

Face ACD should also be differentiated from rosacea, psoriasis, and tinea.

Toes ACD should be differentiated from tinea, palmoplantar dyshidrosiform eczema, and psoriasis. The disseminated disease requires differential diagnosis with erythroderma, such as mycosis fungoides, Sézary syndrome, psoriasis, and pemphigus.

Therapeutic Approach

The most important aspects of the treatment are to remove the contacts and to educate the patient to acknowledge the contact sources and avoid them.

There are databases for consultation by member dermatologists, such as CAMP (Contact Allergen Management Program), operated by the American Contact Dermatitis Society (ACDS) and CARD (Contact Allergen Replacement Database) from the Mayo Clinic [63–67]; more recently in Brazil there is PPAC (www.ppac.com.br). Through these databases, the doctor may provide the patient with a list of products that do not contain the allergen in question so that they can be avoided.

Once parted from the contacts, patients may take a few weeks until they achieve remission.

Repair of the damaged skin barrier through moisturizing is also a crucial factor.

For topical medication, corticosteroids and immunomodulators such as tacrolimus or pimecrolimus can be used.

Phototherapy, such as narrow-band UVB, can be very useful, especially in chronic cases.

For systemic treatment, systemic corticosteroids may be used for short periods if necessary, depending on the severity of the condition.

For chronic and recurrent cases, even when there is longer avoidance of contacts, as in the case of allergy to potassium dichromate, or in cases where there is no other therapeutic option, methotrexate or cyclosporine can be used, bearing in mind their side effects. Methotrexate can be used at a dose of 15 mg/week per os to control the disease. The recommended dose of cyclosporin is between 2 and 3 mg/kg/day orally for 6–8 weeks.

Photoallergic Contact Dermatitis

Etiopathogenesis

Photoallergic contact dermatitis (PACD) is a Gel–Coombs type IV hypersensitivity response resulting from exposure to a photoallergen, with previous sensitization to ultraviolet (UV) radiation. The length of the UV radiation wave is a significant factor for lesion triggering, given that most of the substances require UVA radiation [68, 69].

The photoallergen absorbs the UV radiation, is activated, and releases energy; the molecules then bind to transport proteins and make up complete antigens. The subsequent events are similar to what happens in ACD with participation of specific T lymphocytes [69].

The incidence is unknown for many reasons, among which the diagnostic difficulty related to the tests used for etiologic research.

Clinical Presentation

Symptoms start 24–48 h after exposure with lesions predominantly seen on exposed areas, although covered areas can also be affected in the most acute cases.

Diagnosis and Complementary Examinations

The diagnosis is made through contact phototesting (photopatch test), although there are methodologic variations and variation in interpreting the results of tests.

The methodology is the same used as for the contact test, but the allergens are applied in tandem onto the upper torso, and 48 h later one of the sides undergoes UVA (5–15 J/cm^2) radiation while the other side is protected from the application with opaque material. The radiation equipment is the same used for phototherapy. Reading occurs 48 h after exposure and is compared with the results obtained from the covered side, and follows the same methodology proposed by the ICDRG [48].

Photoallergens

There are many substances involved which depend on the time of the year, the geographic location where they occur, and the habits of affected individuals.

The most common substances are shown in Box 18.5.

Box 18.5 Main PACD Causative Agents
    Photoprotectors
    Topical antibiotics
    Topical antifungals
    Topical anti-inflammatories

Histopathology

The findings resemble those of the ACD, with epidermal spongiosis and dermal mononuclear infiltrate.

Therapeutic Approach

Treatment is based on identification of the causative agent and contact prevention. Identification of UV radiation as a causative agent of the process is extremely important. Therefore, avoiding sun exposure is essential for therapeutic success. When conditions for the exact identification of the etiologic agent are lacking, the use of photoprotectors must be limited since they can also be one of the etiologic agents. The therapeutic treatment follows the same rules as for ACD.

Atopic Dermatitis

Atopic Dermatitis (AD) is an inflammatory skin disease, often related to asthma or allergic rhinitis. It is a condition of chronic and recurrent development, beginning in early childhood as a result of a complex interrelationship between the environment, immunologic and genetic factors [70].

Epidemiology

AD prevalence has increased in recent years from the World War II on, and estimates today report that to up to 20% of the general population is affected [71, 72]. The reason for this rapid increase is still unknown, but is believed to be related to environmental changes [71, 72]. Fabric floor covering in apartments, for example, has increased humidity and buildup of dust, and less space in homes has decreased air circulation and increased conditions favorable for mite propagation [73].

Nearly 50% of all individuals with AD develop symptoms over their first year of life, and possibly 95% may display symptoms before 5 years of age. About 75% will show spontaneous remission before adolescence, whereas 25% will remain symptomatic throughout adulthood [74, 75]. A child with moderate to severe AD has a 50% possibility of developing asthma and a 75% chance of developing allergic rhinitis [76].

Two risk factors seem strongly related with AD development: family history of atopy (two to three times greater possibility with an atopic parent, and three to five times with both parents atopic) [76] and filaggrin gene mutation (*FLG* gene that codifies profilaggrin into filaggrin) in some AD patients. Filaggrin is necessary for the epidermal differentiation and development of the skin barrier, thus impairing skin hydration of those patients presenting with mutation [77].

Etiopathogenesis

The etiopathogenesis of AD is not totally clear, and a complex relationship involving genetic, immune, environmental, psychosomatic, and pharmacologic factors, in addition to changes in the skin structure itself, have been shown. The two main DA disorders are dysfunctional skin barrier and immunologic reaction, both interrelated, thus triggering a vicious circle.

Skin Barrier Change

The skin barrier comprises the stratum corneum that is made up of a double heterogeneous compartment, of which the main elements are corneocytes and extracellular lipids. The extracellular lipids of the stratum corneum are basically composed of ceramides (45–50%), cholesterol (25%), and free fatty acids (10–15%). The ceramides are crucial to the barrier function. One of the main roles of the skin barrier is permeability control. When this function is lost the skin undergoes physical, chemical, and biological aggression [78].

AD xerosis, or dry skin, is related to changes in epidermal differentiation, the epidermal lipid metabolism, and increased transepidermal water loss [79].

Immunological Changes

AD is an inflammatory biphasic skin disease characterized by an early phase when there is prevalence of T-helper 2 (Th2) cytokines and a later chronic phase when Th1 is prevalent.

The antigens that penetrate the epidermis resulting from a decrease of the skin barrier function are captured by the IgE molecules via receptors of the Langerhans cells (LCs), which are the main cells that introduce the epidermis antigens. The antigen is internalized and processed. The LCs introduce antigens to the Th2 lymphocytes, which start the cytokine synthesis (IL-4, IL-5, IL-13, and IL-16). IL-4 stimulates the B lymphocytes to produce IgE, while IL-5 induces the eosinophil synthesis and maturation [80, 81].

The mastocyte-related IgE brings about their degranulation by releasing their mediators, such as histamine, thereby causing pruritus and edema noticed during the AD acute phase. In the chronic phase a change in the cytokine pattern by the T lymphocytes occurs from the Th2 to the Th1, freeing IL-12 [82].

Many etiopathogenic factors in AD remain a controversial issue. *Staphylococcus aureus* is considered a triggering and/or aggravating factor, able to be isolated from the skin in 90–100% of sick individuals who undergo the specific IgE synthesis [83]. Most AD patients display high levels of total IgE with part of this IgE oriented against domestic dust mites [84]. It has been shown that contact with air allergens can exacerbate AD, with *Dermatophagoides pteronyssinus* as the main representative allergen [85]. Intra- and extradomestic home fungi have also been involved in the condition, as well as skin colonizers such as *Candida albicans*, *Malassezia furfur,* and *Trichophyton* spp. [84]. Emotional stress can also exacerbate AD, although the exact mechanism of the skin immune system and the nervous system interaction has not been identified yet; it is believed that such a phenomenon is mediated by neuropeptides [86].

Diagnostic and Clinical Presentation

No laboratory or histologic test has been described; therefore, the diagnosis is based on clinical characteristics. The most frequently used diagnostic criteria were developed by Hanifin and Rajka in 1980 [70], and reviewed in 2004 by the American Academy of Dermatology (AAD) [87]. Box 18.6 presents the Hanifin and Rajka criteria for AD.

Box 18.6 AD Diagnosis
Essential features:

Itch
Eczema with typical morphology and age-specific pattern

Important features:

Early age of onset
Atopy (family or personal history)
Dry skin

Related characteristics:

Atypical vascular response (facial pallor, white dermographism)
Keratosis pilaris, palmar hyperlinearity, ichthyosis
Ocular and periorbital changes
Other regional findings (perioral or periauricular lesions)
Perifollicular accentuation, lichenification, and excoriations

Developed by Hanifin and Rajka and modified by the AAD [70, 87].

AD injuries are no different from those of other eczemas such as contact eczema. In severe forms, erythema, edema, vesicles, oozing and crusts, lichenification, abrasions, papules, and nodules dominate the subacute and chronic forms. The typical AD patient is a person which has "an eczematous, pruriginous, early beginning disease, typically located in the antecubital and popliteal flexures of a patient with atopical or family readiness disease" [88]. Box 18.7 presents the phases of DA.

AD has a chronic course in many patients because of the difficulty in predicting periods of activity or discerning the aggravating factors. Some patients are sensitive to woolen clothing, which aggravates itching, hot water and longer showers/baths that aggravate the symptoms and the xerosis; therefore, they must be avoided. Some staphylococcal infections may trigger crises. Food must not be avoided unless the patient has a confirmed allergy. There are reports of worsening symptoms caused by life stress [88].

The most frequent complications are *S. aureus* secondary infections, herpesvirus infection resulting in herpetic eczema (widespread vesicular eruption on the face, scalp, and upper chest), mainly in severe forms of the disease, and molluscum contagiosum.

Differential Diagnosis

An AD-resembling eruption can be seen in many diseases, but a careful evaluation of the morphology and localization of the rash combined with information about each patient often leads to the correct diagnosis [87]. Box 18.8 lists diseases that must be left out.

Complementary Tests

The diagnosis of AD remains clinical because there are no reliable biomarkers that can distinguish it from other diseases. The most commonly associated laboratory feature, an elevated total and/or allergen-specific serum IgE level, does not affect about 20% of individuals. The prick test (immediate puncture test) is useful mainly when it results as negative to some allergens, thus removing its participation in the disease origin [89]. The contact test for atopy (atopy patch test) is a new procedure still being standardized; the most advanced tests aim at the *Dermatophagoides pteronyssinus and farinae* mites [90].

Histopathology is typical to eczema; hyperkeratosis and papillomatosis are prevalent in the chronic lesions.

Therapeutic Approach

Nonpharmacologic Interventions

Xerosis resulting from a dysfunctional skin barrier is one of the characteristics of the AD patients. The use of an emollient and a moisturizer (glycerin, for example) lubricates and softens the skin. Occlusive-acting emollients (vaseline, dimethicone) make a barrier to delay water evaporation. Using a formula with these two types of substance is effective and must be applied two to three times a day. Its use decreases AD signs and symptoms, such as pruritus, erythema, fissures, and lichenification, as well as

the need for pharmacologic intervention [91]. The use of urea and ammonium lactate at high concentrations has to be avoided as they can result in skin rash; scent moisturizers must also be avoided.

Showers (baths) are useful for skin crust and rash agent removal; tepid and quick (5 min) showers (baths), with little soap, are recommended to preserve most of the skin barrier. A moisturizer must be applied to the skin immediately after the shower (bath) [92].

Light clothes are also recommended to avoid excessive sweating leading to pruritus. Cotton clothes are suggested. The patient's environment has to be airy, with no carpets or curtains, to make cleaning easy.

The wet-wrap technique may be used, with moisturizer or topical corticosteroids, consisting of the applying the agent followed by occlusion with a wet bandage and subsequent dry bandage. The topical-corticosteroid bandage is more effective when compared with the use of moisturizer only, but care has to be taken regarding adverse effects [93].

Topical Corticosteroid Therapy

Topical corticosteroids are anti-inflammatory agents that control pruritus and eczematous lesions by inhibiting the dendritic cells and lymphocyte activity, thereby avoiding interleukin synthesis. The most common local adverse effects include purpura, telangiectasia, striae, and cutaneous atrophy.

Corticosteroid therapy is recommended to patients who have failed emollient treatment. A range of factors has to be considered for prescription, such as age, application sites, costs, and patient preferences. Application usually occurs twice a day. A proactive treatment can be made when the corticosteroid is applied for two consecutive days, over a week, on the affected areas, even when there is no active lesion, to prevent new crises. As the genital area, the face, and the folded areas display high absorption rate, low- or medium-potency corticosteroids are recommended for use on these areas. Monitoring of local adverse effects is advisable [94].

Topical Immunomodulators

Calcineurin inhibitors are a class of drugs used in AD. Calcineurin is found in the lymphocytes acting in the inflammatory interleukin transcript.

There are two calcineurin inhibitors for topical use: 1% pimecrolimus (from 3 months old), 0.03% tacrolimus (from 2 years old), and 0.1% tacrolimus (patients older than 15 years of age). Given twice a day, they do not have the side effects of corticosteroids and can be used for longer periods, even on the face. Their most widely known side effects are pruritus and burning. A relationship between topical use and systemic immunosuppression and malignancy has not been established. These agents can be used in proactive treatment with topical corticosteroids [95–97].

Phototherapy

Phototherapy is a second-line treatment used in the absence of topical corticosteroids or calcineurin inhibitors, and can be useful for maintenance of chronic patients. UVB narrow band, UVA 1, and PUVA (UVA + psoralen) can be used by physicians with experience in these techniques. The therapeutic approach must take into account factors such as availability, costs, phototype, and family history of skin cancer. Local erythema, pruritus, and burning are the most often seen adverse effects; nonmelanoma skin cancer; melanoma, and lentigo are seldom seen [98].

Systemic Immunosuppression

Systemic immunosuppression is used for those patients who do not respond to the usual treatment.

Cyclosporin

Cyclosporin is the most assessed substance in research studies in both adults and children, in intermittent and continuous courses. The standard doses vary from 3 to 6 mg/kg/day, over 12 weeks, which may be repeated after a 7-day interval or sustained for 1–2 years. Unfortunately, recurrence ensues after treatment interruption. Periodically the renal function, arterial pressure, and cyclosporine serum levels should be monitored [99].

Azathioprine

Azathioprine is used at a 1–3 mg/kg/day, for 12 weeks or more, until the clinical benefit is reached, with AD improvement from 25% to 37%. Nausea, vomiting, and anorexia are the most frequent side effects. There are reports of hepatic enzyme increase, leukopenia, cephalea, and even lymphoma in patients treated with this agent [100].

Methotrexate

Methotrexate is an antifolate metabolite that blocks DNA, RNA, and purine synthesis, whose efficacy in treating AD remains unknown. Some studies have shown improvement in 52% of patients who used the drug over 24 weeks. The regimen varies from 7.5 to 25 mg/week, divided into three doses, with a 12-h break between each. Improvement is often noticed in the tenth week of treatment, and once obtained the dosage must be tapered until its discontinuation. Nausea and other gastrointestinal symptoms are the most common adverse effects. Hepatotoxicity needs to be monitored. Folic acid supplementation is suggested to reduce hematologic and gastrointestinal toxicity [101].

Oral Antimicrobials

Antibiotics have to be used when there is clinical evidence of bacterial infection (*S. aureus*), or antivirals when herpetic eczema caused by the herpes simplex virus is diagnosed, in combination with traditional treatment for AD [102, 103].

Oral Antihistamines

Oral antihistamines do not show properly verified clinical benefits, and have been used for their sedative effect, thus improving the quality of sleep [104].

Oral Corticosteroids

Oral corticosteroids are used by some physicians to rapidly improve clinical symptoms. Rebound flare and worsening of the disease severity are observed phenomena after drug discontinuation. Although temporarily effective, this treatment must be avoided in both adults and children because of the potentially adverse effects over short-term use. Oral corticosteroids may be used for short periods in cases where another systemic treatment or phototherapy has been started or optimized. Hypertension, glucose intolerance, gastritis, weight gain, and adrenal suppression are the most common adverse effects [105].

Other drugs, such as mycophenolate mofetil and IFN-γ, have been used in trials involving a small number of patients, with improvement noticed in certain cases [87].

Support Groups

A support group is an extremely valuable measure, since AD patients and their families often need a multidisciplinary approach that comprises not only the physician but also other specialty area professionals, mainly psychologists and nurses. Furthermore, it is an opportunity to share the complexity of a chronic disease that affects their quality of life with individuals and relatives going through a similar life experience [106, 107].

Nummular Eczema

Introduction

Nummular eczema, which has received this name because of the lesion's clinical aspect, of a round or oval shape resembling coins. Marie Guillaume Alfonse Devergie described it during the mid-1990s [108].

It is an idiopathic, inflammatory, and recurrent dermatosis with pruritus as its most prevalent clinical sign.

Epidemiology

Nummular eczema is more often found in male adults, although peaks of incidence occur both in men and women from the ages of 50 to 65 years [108].

Etiopathogenesis

The etiology is unknown, although many isolated or associated factors – nutritious, infectious, and emotional – are involved in its genesis. It is already known that the dermatosis is more frequent in alcohol-abusing individuals [109]. It can also be an atopic dermatosis manifestation during childhood.

Dry skin may be a significant etiologic factor mainly among older individuals, an occurrence that makes the interruption of skin barrier easier.

The fibrinogen and fibronectin bacterial receptors in these patients bestow more pathogenic adherence, thus promoting early and persistent *S. aureus* skin colonization [110].

Some drugs, such as gold, isotretinoin, pegylated IFN-α2b, ribavirin, and, more recently, infliximab, are associated with the appearance of nummular eczema [111, 112].

Contact allergens can aggravate or induce the primary lesions. Frequency of sensitization has varied from 30.1% to 77.9% in different studies. The most commonly involved allergens are nickel, potassium bichromate, cobalt chlorate, paraphenylenediamine, ethylenediamine, and neomycin. The authors have suggested the study of contactants mainly in chronic and treatment-resistant cases [113].

Clinical Presentation

Dermatosis can occur on any part of the tegument, although the torso and the lower limbs are the preferred parts. Papules and papulovesicles make up well-delimited plates of varied sizes. Oozing and crust-composition areas can be seen. Chronic plates are dry, scaling, and lichenified (Fig. 18.11).

Fig. 18.11 Nummular eczema

Differential Diagnoses

The diseases that may lead to confusion with nummular eczema are summarized in Box 18.9.

> **Box 18.9 Differential Diagnoses for Nummular Eczema**
> Allergic contact dermatitis
>   Stasis dermatitis
>   Atopic dermatitis
>   Tinea corporis
>   Mycosis fungoides (old lesions)
>   Paget disease (unilateral involvement of the nipple/areola)
>   Fixed drug eruption
>   Pityriasis rotunda

Therapeutic Approach

Treatment involves the use of topical corticosteroids of medium strength, although the calcineurin inhibitors tacrolimus and pimecrolimus play a major role in cases of longer treatment. Emollients are key when there is concomitant xerosis, but not before improvement of the oozing lesion if it is present.

Oral antihistamines are important for decreased pruritus. Systemic antibiotics are indicated when conspicuous secondary infection is seen. For extensive or traditional treatment-resistant forms, good results can be obtained with UVB narrow-band phototherapy.

Stasis Dermatitis (Stasis Eczema)

Introduction

Stasis dermatitis or eczema is a chronic condition often seen on the lower limbs, resulting from venous stasis. It is more often found in women than in men. The most frequent cause of venous stasis is lower limb varices, resulting from vascular insufficiency or thrombophlebitis. Other factors, such as obesity, congenital skeletal and muscular alterations, lower limb fractures, and planovalgus feet are involved.

Etiopathogenesis

In cases of lower limb varices, the inability of venous valves increases the intravascular pressure, leading to its insufficiency, thereby leading to pitting edema caused by fluid extravasation. Varicose varices can become evident mainly on the malleolar regions. Hyperpigmentation occurs in the same region, owing to hemosiderin deposition from extravasated red blood cells, a process that may reach all of the limb affected [114]. Chronic edema can present abrupt worsening episodes; the skin becomes erythematous and scaly, and the diagnosis can be confused with erysipelas/cellulitis.

Chronic venous stasis changes microcirculation inducing fibrinogen extravasation through the venules and the consequent deposition of pericapillary fibrin, thus making a barrier for the diffusion of oxygen and other nutrients and thereby resulting in stasis dermatitis that can ultimately lead to tissue necrosis and ulcer formation [115].

Clinical Presentation

Clinically, stasis dermatitis is manifested as acute, subacute, and chronic eczema. Symptoms such as pruritus are conducive to exulceration. Exulcerations make bacterial infections more likely, which may evolve to erysipelas, a common complication in such cases. Lipodermatosclerosis is another complication that also mimics cellulitis/erysipelas, a condition resulting from necrosis and fibrotic inflammation of the subcutaneous cellular tissue. The acute form occurs with localized pain mainly in the lower third of the legs. It has a slow evolution and can be bilateral, conditions that make it different from cellulitis. Skin hyperpigmentation and stiffness can be seen in the chronic forms,

Fig. 18.12 Stasis dermatitis

which compress the ankle region thus creating an inverted champagne-bottle shape. The aggravating crises can overlap in the chronic forms [114] (Fig. 18.12).

Therapeutic Approach

The acute forms of dermatitis have to be treated with topical or systemic corticosteroids over a short period of time. The use of emollients can be encouraged mainly in cases of concomitant localized xerosis. The edema can be controlled with interventions such as limb elevation above

heart level, which is not always possible at home. Compressive methods, such as the Una boot or compression stockings, make the venous return easier and are useful for presentation control [116].

Dyshidrotic Eczema

Introduction

Dyshidrotic eczema, or pompholyx, is a form of recurrent eczema more often found on the palmoplantar regions. The early suggested nomenclature refers to the presence of multiple vesicles on the affected regions; the alteration is due to the presence of intraepidermic spongy vesicles and not to the eccrine sweat glands that heavily populate the area.

Epidemiology

Universal dermatosis can affect both men and women mainly in their twenties to forties [117]. Some studies estimate its prevalence from 0.05% to 10.6% of the population [118]. In 2006, a Chinese study [119] identified a family with an autosomal dominant type of pompholyx, a genetic locus in the 18q22.1–18q22.3 chromosomes between the D18S465 and D18S1362 markers. Most cases are sporadic.

Pathogenesis

The exact mechanism that accounts for the vesicles' development is still unknown, although various factors are implicated in their pathogenesis, such as contact dermatitis (nickel, cobalt, Balsam of Peru, *p*-phenylenediamine, rubber vulcanization agents), atopic dermatitis, drug eruption (highly active antiretroviral therapy, piroxicam, immunoglobulin), distant hypersensitivity reaction resulting from fungal infection (feet tinea due to dermatophytes), and post-HIV infection [120].

Other factors are seen as aggravating conditions of the disease, such as tabagism, stress, and longer use of protective gloves [117, 120].

Soler and cols. have recently studied the role of the aquaporins (AQP) in the dyshidrosis pathogenesis. They found that excessive expression of AQP3 and AQP10 occurs in the affected areas of the dyshidrotic patients, a fact also noticed in AD patients [121].

The AQP are proteic channels that increase cell membrane malleability bidirectionally and osmotically driven for small molecules, such as water, glycerol, and urea. They regulate skin moisture by changing the TEWL, which plays a major role in disease intensity and aggravation [121].

With tissue water loss, changes in the protease balance occur which degrade the desmosomes, leading to an increase in the intracellular calcium concentration and activation of the transglutaminases involved in corneocyte maturation. These effects increase xerosis, resulting in aggravation of dermatosis [121].

Clinical Presentation

Dyshidrosis can be classified as idiopathic or true, and also as dyshidrosiform eruption if associated with other dermatoses (contact dermatitis, AD, drug eruption, or ICD).

It is characterized by the presence of vesicles with clear and colorless content on the palmoplantar area, with no erythema, mainly located on the lateral and dorsal areas of the fingers. They can be grouped and turn into blisters. Secondary infections are a common complication (Fig. 18.13).
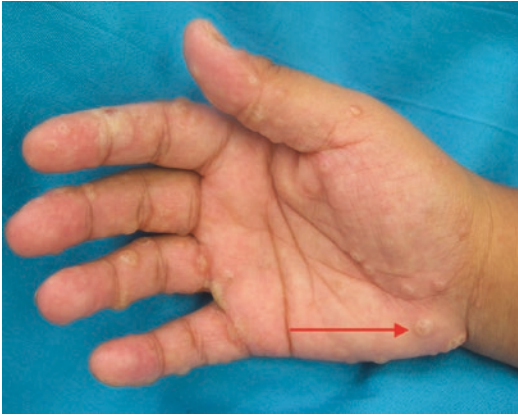
Fig. 18.13 Dyshidrotic eczema

Diagnosis

The diagnosis is based on a detailed anamnesis and observation of recent recurrent outbreaks. Research on the associated factors must be conducted by direct mycologic examination of the feet vesicles, presence of the diagnostic criteria for AD, investigation of ingested drugs before the beginning of the disease, and contact tests in the chronic cases.

A biopsy may be needed to confirm the diagnosis or to omit other diseases considered in the differential diagnosis.

Differential Diagnosis

Many cutaneous diseases may mimic dyshidrotic eczema (see Box 18.10).

Box 18.10 Differential Diagnoses for Dyshidrotic Eczema

Acropustulosis of childhood
 Lymphoma/T-cell adult leukemia
 Bullous impetigo
 T-cell bullous lymphoma
 Dyshidrosiform pemphigoid
 IgA linear dermatosis with dyshidrosis
 Bullous epidermolysis
 Erythema multiforme
 Hand-foot-mouth disease
 Herpes simplex

Fixed drug eruption
Attrition blisters
Pemphigus vulgaris
Pustular psoriasis
Scabies
SAPHO syndrome

Therapeutic Approach

Disease management is difficult and encompasses general measures, such as quitting tobacco; proper hand and foot drying; hand washing when strictly necessary; avoidance of direct contact with soaps, detergents, fresh fruit, and meat; use of protective gloves even during hair shampooing; and use of cotton socks with frequent and regular changes. Topical or systemic drugs may be indicated depending on the acuteness of the condition.

Topical corticosteroids or calcineurin inhibitors can be an option to contain new vesicle development. Associated measures are sometimes necessary, such as the use of medication under occlusion. Bexarotene gel 1% has been described as a therapeutic option, either in isolation or combined with topical corticosteroids.

Systemic treatments can be implemented in the more acute forms, or in the nonreactive forms for topical drugs, when drugs such as corticosteroids (prednisone) can be used for limited periods to avoid unwanted adverse effects. Immunosuppressive drugs, such as azathioprine (100–150 mg/day) and methotrexate (15–25 mg/w), can be useful, as well as mycophenolate mofetil (2 g/day).

Antihistamines are important for symptom control. Botulinum toxin type A is applicable in cases when hyperhidrosis is an aggravating factor (162 U per palm). UVB narrow-band phototherapy (311 nm) and UVA-1 (320–400 nm) are considered good therapeutic options.

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Psoriasis

André Vicente Esteves de Carvalho

Key Points
- Psoriasis is an immune-mediated inflammatory disease whereby erythematous scaling plaques appear on otherwise healthy skin
- Besides skin lesions, psoriatic patients may develop arthritis and are prone to developing several other comorbidities
- Immunosuppressive and immunomodulatory treatment targeted to key molecules in psoriasis pathophysiology are highly efficacious in treating severely affected patients

Epidemiology

The prevalence of psoriasis may range from 0.4% to as much as 4.7% depending on the population studied. Some reviews found that the prevalence among Africans (and African Americans), Norwegian Lapps, and Asians to range from 0.4% to 0.7%, whereas Americans (United States) and Canadians have a prevalence of 4.6% and 4.7%, respectively. In general it is accepted that 2% of the world's population may suffer from the disease and two-thirds of these patients develop a mild form of psoriasis, whereas one-third will have the severe form of the disease [1–3].

There is no difference between genders regarding psoriasis prevalence. Alcohol and tobacco consumption is thought to be associated with the development of lesions in men. The disease may arise in any age group, and cases have been described in infants and in the elderly, but two peaks of onset have been reported, the first between 15 and 30 years of age and the second between 50 and 60 years. Seventy-five percent of patients develop first lesions before the age of 40 [4]. Pustulosis of the palms and soles, a form of localized pustular psoriasis, differs in its epidemiology from the other clinical presentations of psoriasis. It tends to present at a later stage of life, affects more females than males, and is highly associated with tobacco consumption [5].

Arthritis may be found in up to 30% of psoriatic patients, and nail psoriasis, a known risk for arthritis development [6], occurs in almost 80% of psoriatic patients [7]. AIDS patients frequently develop psoriasis, and the prevalence of the disease is higher when the CD4$^+$ T-lymphocyte cell count falls below 200 cells/mm. Studies of HIV-positive patients show a 4% increased psoriasis prevalence over that of the general population [8].

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Having psoriasis may be a risk for developing associated comorbidities, such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, nonalcoholic fatty liver disease, high blood pressure, diabetes, high levels of blood lipids, and obesity (metabolic syndrome) [9]. The inflammatory burden that follows the psoriasis onset, together with the deleterious effect of the comorbidities, especially metabolic syndrome, increase the risk for death by acute myocardial infarction in severe psoriatic patients, this risk being higher for younger patients. After 60 years of age, the role of psoriasis in cardiovascular risk is overtaken by the risk of the components of the Framingham risk score [10, 11]. The prevalence of depression and suicidal ideation is also higher among psoriasis patients [9].

Etiopathogenesis

Psoriasis is an immune-mediated systemic inflammatory disease of polygenic origin that is triggered by several environmental factors (see Box 19.1) mainly affecting the skin. The major candidate gene for psoriasis is *HLA-Cw6* (locus PSORS1), although several others are implicated [12] (see Box 19.2). Family history of psoriasis is described in at least 35% of patients, although some studies report up to 90%. When both parents are affected, the risk of psoriasis on the offspring seems to be 41%, whereas it is 14% if only one parent is affected [13, 14].

Box 19.1 Factors Triggering the Development/Worsening of Psoriasis
- Physical stress/trauma (Koebner phenomenon)
- Psychogenic stress/trauma
- Infections
  - Bacterial (streptococcal, staphylococcal)
  - Viral (HIV/AIDS)

- Drugs
  - Antimalarials
  - β-Blockers
  - Systemic corticosteroids (after rapid withdrawal)
  - Interferons
  - Lithium
  - Terbinafine
- Pregnancy (impetigo herpetiformis)
- Hypocalcemia (inducing general pustular psoriasis)
- Alcohol and tobacco consumption
- Obesity

Box 19.2 Major Genetic Loci Associated with Psoriasis
- *PSORS1* (includes HLA-Cw6)
- *PSORS2*
- *IL-12B*
- *IL-23A*
- *IL-23R*
- *CARD14*
- *CDKAL1*
- *NFKBIA*
- *TNFAIP3*
- *TNIP1*

Since the introduction of cyclosporine as an antipsoriatic drug [15], it has been known that psoriasis is an immune-mediated disease rather than a disorder of keratinization. In fact, the hyperkeratosis featured in the psoriatic lesion has an underlying immune imbalance that explains its development [15]. A dysregulation between the innate and the adaptive immunity, mediated through specific resident cutaneous cell types (such as dermal plasmacytoid dendritic cells) and a cascade of proinflammatory cytokines (interleukin (IL)-17, IL-23, and tumor necrosis factor α (TNF-α)), for example [14].

Fig. 19.1 Plaque type psoriasis. Characteristic erythematous scaling lesion on typical sites, such as the elbow

The initiation of the process is thought to be the stimulation of plasmacytoid dendritic cell in the dermis by a complex formed by the antimicrobial peptide LL-37 (cathelicidin) and the host DNA. Stimulated plasmacytoid dendritic cells produce interferon-(IFN)-α, which activates dermal dendritic cells, hence the current supposition that IFN-α is a key factor in the beginning of the disease and in its flares [16]. Activated dermal dendritic cells migrate to the lymph node where, stimulated by IL-6 and transforming growth factor β, it acts to differentiate naive T lymphocytes into specific subsets of T-helper cells called Th1, Th17, and Th22. The maintenance of the Th17 response is achieved through IL-23 release, making this cytokine a target for the treatment of chronic stable psoriasis [17, 18]. This Th1, Th17, and Th22 cells subset travel through the circulation until being recruited via a series of chemokines and cytokines to act on specific sites of the skin. There they amplify inflammation through the release of TNF-α and IFN-γ, with subsequent release of a cascade of proinflammatory cytokines such as keratinocyte growth factor, epidermal growth factor, and vascular endothelial growth factor, leading to vasodilatation, ectasia, keratinocyte stimulation, and epidermal proliferation. This process represents the underlying etiology of the clinical features seen on psoriatic plaques: redness, infiltration, and scaling [7] (Fig. 19.1).

Clinical Presentation

The characteristic lesion is a red, scaly, infiltrated lesion with well-demarcated borders, although the clinical features may vary among the distinct forms of the disease. Typical sites for the development of lesions are the scalp, elbows, and knees, although they can also frequently appear on the genitals and the lower back. Extension of the disease may range from a single lesion to erythroderma (all or almost all the skin is affected). Acute flares and unstable lesions tend to show prominent signs of inflammation with an intense erythema but less desquamation and infiltration. Pinpoint erythematous lesions around a previous plaque may be a sign of expansion of

the disease. Sometimes, if the inflammatory infil-
trate is important, pustules may arise and the
lesion may be tender or itchy. Chronic stable
lesions present variable degrees of erythema,
scaling, and infiltration. Itching is variable on
chronic lesions [1, 7].

The subtypes of the disease are as follows.

– *Plaque type psoriasis*

The most common type of the disease, plaque
type psoriasis is characterized by round or oval
erythematous, infiltrated scaly lesions that may
vary in size from a few centimeters to large con-
fluent plaques that may affect almost all the skin
surface. According to the extension of the dis-
ease it can be classified as localized (<10% of
the body surface area (BSA)) or generalized
(≥10% of BSA). Knees, elbows, scalp, genitalia,
and the lower back are usually involved. Lesions
on the palms and soles can be painful and be a
cause of social embarrassment or work absentee-
ism. Lesions tend to resolve leaving a hypochro-
mic patch, especially on darker-skinned
individuals [2, 19] (Figs. 19.1, 19.2, 19.3, 19.4,
and 19.5).

– *Guttate psoriasis*

Guttate psoriasis is a subtype of the disease
whereby an abrupt eruption of small (0–2 cm
diameter), round, erythematous, scaly plaques
appear usually after a streptococcal upper respi-
ratory tract infection. It affects children and
young adults, being less frequent in older indi-
viduals. Antistreptolysin, streptozyme, and anti-
DNase B titers can be found in the blood,
corroborating a previous occurrence of a strepto-
coccal infection [19].

– *Erythrodermic psoriasis*

Erythrodermic psoriasis is a generalized vari-
ant (>90% of the body surface area affected)
characterized by intense erythema and scaling
and little to no infiltration. Pruritus can lead to
scoriation. The face is usually spared and sys-
temic corticosteroid withdrawal is a known pre-
cipitant (see Box 19.1). It is a critical condition,
usually leading to hospitalization because of
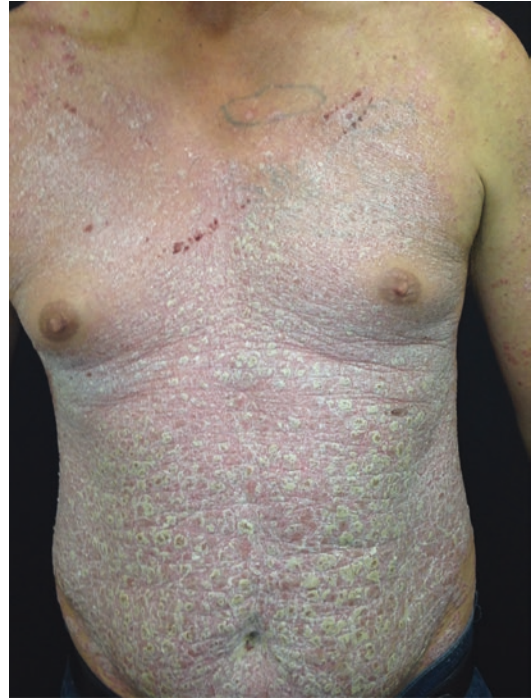
Fig. 19.2 Generalized plaque type psoriasis

Fig. 19.3 Plaque type psoriasis resolving phase. Lesions
with a central resolving white patch and a tricophytoid
appearance

Fig. 19.4 Palmoplantar psoriasis: Palmar lesions showing erythema, scaling, and little infiltration. Lesions tend to lead to painful fissures

Fig. 19.5 Plaque type psoriasis. Typical scalp and retro-auricular lesions

Fig. 19.6 Erythrodermic psoriasis. Lesion on 90% or more of the body surface area. Note that erythema and scaling are prominent over infiltration

impairment of the skin's barrier function and further hydroelectrolytic imbalance. Fever or hypothermia may be signs of systemic infection [7] (Fig. 19.6).

– *Generalized pustular psoriasis*

Several sterile pustules arise from an intensely erythematous skin, without scaling. The von Zumbusch subtype is a much more severe form of the disease and, as in the erythrodermic form, leads to hospitalization. Sometimes if not well treated it may lead to death, mainly by subsequent infection. The patient may experience fever and malaise. Withdrawal or rapid tapering of systemic corticoids is the main triggering factor.

Pregnancy, infections, and hypocalcemia are also precipitants. IL-8 and IL-1β are involved and IL-36 gene receptor antagonist may be found in some of these patients. Impetigo herpetiformis is a form of generalized pustular psoriasis that affects pregnant women. It may represent a risk for the fetus and preterm labor, and miscarriages eventually can occur. A more restricted form ("localized") of pustular psoriasis can occur over pre-existing lesions, on the outer edges of the plaques, especially in unstable disease. An annular subtype is described as pustules and scaling on the advancing borders of the plaque, while the center of the lesion can be spared or show advanced healing. The exanthematic variant may arise abruptly after triggering factors such as infections or lithium. It may also overlap with other pustular drug-induced eruption, such as AGEP (acute generalized exanthematous pustulosis) [1, 19].

– *Palmoplantar pustulosis*

Classification of palmoplantar psoriasis is controversial as it is a disease without PSORS1 (HLA-Cw6) positivity. Its association with tobacco smoking and metal allergy also led some authors to consider palmoplantar pustulosis as a separate entity [5]. On the other hand, the fact that 18% of patients show characteristic lesions of plaque-type psoriasis elsewhere in the body and 20% present a family history of psoriasis are arguments in favor of classifying the disease as a subset of pustular psoriasis [20]. Sterile pustules arise over erythematous or even clear skin and are limited to the palms and soles, with predilection to the cavum. Pustules may coalesce to form lake-like collections in severe cases. Resolving lesions leave brownish macules [21] (Fig. 19.7).

– *Acrodermatitis continua of Hallopeau*

This is a rare subtype of localized pustular psoriasis that affects the tips of the fingers. Toes are less affected. The involvement of one or two fingers is usual. Sterile pustules arise in the fingertips, sometimes involving the entire fingertip including the nail bed, leading to the destruction of the nail unit. Lesions resolve with crusts, and sometimes bone reabsorption of the distal phalanx can occur if the inflammation is intense and chronic [21].

– *Flexural psoriasis*

Also called "inverse," flexural psoriasis can affect 2–6% of all psoriatic patients. Lesions are shiny erythematous plaques with variable infiltration and almost no scaling. The absence of desquamation is a valuable diagnostic clue and is due to maceration of the horny layer caused by humidity and friction of the flexural areas. Axillae, intergluteal cleft, inframammary region, and inguinal crease are commonly affected areas [7] (Fig. 19.8).

– *Nail psoriasis*

The nail can be affected in up to 80% of psoriatic patients and is a risk factor for the develop-

Fig. 19.7 Pustular psoriasis. Localized palmoplantar lesions. Pus is formed by intense exudation of neutrophils

Fig. 19.8 Inverse psoriasis on the axillae

ment of psoriatic arthritis. The clinical manifestation depends on where the inflammation affects the nail unit: matrix, nail bed, and hyponychium. Onycholysis (separation of the nail plate from the nail bed), "oil spots" (inflammatory

Fig. 19.9 Nail psoriasis. Onycholysis and nail pitting

exudate from the nail bed), nail pitting (dome-shaped depressions of the nail plate caused by altered keratinization of the proximal matrix), and subungual hyperkeratosis (altered keratinization of the nail bed) are common signs [22] (Fig. 19.9).
– *Psoriatic arthritis*

Presently characterized as a seronegative spondyloarthropathy, psoriatic arthritis is, in most cases, an asymmetric mono- or oligoarthritis. Up to 30% of psoriatic patients can develop arthritis. Nail psoriasis, intergluteal psoriatic lesions, and scalp psoriasis are thought to be risk factors. The most common sites affected are the proximal and distal interphalangeal joints of the hands and feet. The arthritis almost invariably begins as an enthesitis, which may result in a swollen digit called "sausage finger." Rheumatoid factor is almost invariably negative and metacarpal involvement, typical of rheumatoid arthritis, is also absent. Exclusive disease of distal interphalangeal joint can lead to rigidity of the joint in a flexed position, and nail psoriasis is often present. Axial arthritis can occur, resulting in spondylitis and sacroiliitis, which occurs along HLA-B27 positivity. Larger joints such as the knee and the ankle are also affected, and enthesitis of the Achilles tendon is sometimes the first manifestation of the disease [7, 23, 24].

Diagnosis

The diagnosis of psoriasis is eminently clinical. The presence of a characteristic lesion at preferential sites is usually enough to confirm the suspicion. The Auspitz sign (methodic curettage of silver scales leading to bleeding through pores), Koebner phenomenon, and nail lesions may help consideration of psoriasis. Resolving psoriatic lesions may resemble tinea, as they may become tricophytoid, with an "active" border circumscribing an already healed center. Palmoplantar lesions also can be misinterpreted as tinea pedis. In both cases, a scraping with further direct examination and culture can elucidate the case. As candidiasis may be confounded with flexural psoriasis, KOH examination for yeasts can elucidate the diagnosis. Nevertheless, the concomitance of candidiasis and flexural psoriasis is often seen. Other erythematous squamous diseases that can mimic the clinical features of psoriasis can be investigated through a skin biopsy [7].

The severity of the disease is usually measured in clinical trials by the Psoriasis Area and Severity Score (PASI), a score that ranges from 0 to 72; patients with a score of 10 or higher are considered as having a severe disease (Table 19.1). The PASI is also used to evaluate response to treatments, and a usual primary endpoint in clinical trials that evaluate antipsoriatic drugs is the PASI75 (75% improvement over baseline PASI). Other instruments to measure severity are also used, such as the BSA and the Physician's Global Assessment (PGA). The DLQI (Dermatology Life Quality Index) is a self-administered 10-question questionnaire that ranges from 0 to 30 and evaluates the impact of any dermatology condition on the quality of life. A score of 10 or more determines that the disease has major impact on the patient's quality of life [25].

Diagnosis of psoriatic arthritis is made using the CASPAR criteria (Table 19.2) and the efficacy of treatment in most clinical trials is measured by the American College of Rheumatology score (ACR 20) [26].

Table 19.1 Psoriasis Area and Severity Score (PASI)

	Erythema[a]	Induration[a]	Scaling[a]	SUM	X Area[b]	Result	Factor[c]	Total
Head							0.1	
Upper limbs							0.2	
Trunk							0.3	
Lower limbs							0.4	
Total PASI								

[a]*Severity*: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4, very severe
[b]*Area*: 0 = none, 1 = <10%, 2 = 10–29%, 3 = 30–49%, 4 = 50–69%, 5 = 70–89%, 6 = 90–100%
[c]Correction factor for each body region

Table 19.2 Cl**AS**sification criteria for **P**soriatic **AR**thritis (CASPAR) criteria

To be classified as having psoriatic arthritis, patient must have inflammatory articular disease (joint, spinal, entheseal) with 3 or more of the following 5 points:	
Criterion	*Description*
1. Evidence of psoriasis (one of a, b, or c):	Psoriatic skin or scalp disease currently present, as judged by a dermatologist or a rheumatologist
(a) Current psoriasis[a]	
(b) Personal history of psoriasis	A history of psoriasis obtained from patient or family physician, dermatologist, rheumatologist, or other qualified healthcare professional
(c) Family history of psoriasis	A history of psoriasis in a first- or second-degree relative by patient report
2. Psoriatic nail dystrophy	Typical psoriatic nail dystrophy, including onycholysis, pitting, and hyperkeratosis observed on current physical examination
3. Negative test result for rheumatoid factor	By any method except latex but preferably by ELISA or nephelometry, according to the local laboratory reference range
4. Dactylitis (one of a, b)	Swelling of an entire digit
(a) Current	A history of dactylitis recorded by a rheumatologist
(b) History	
5. Radiologic evidence of juxta-articular new bone formation	Ill-defined ossification near joint margins (excluding osteophyte formation) on plain X-ray films of hand and foot

All other items score 1
[a]Current psoriasis scores 2

Complementary Examinations

The pathologic examination of a stable psoriatic lesion classically reveals acanthosis with elongated rete ridges ("clubbing"). The horny layer is thicker than normal skin and focal parakeratosis with hypogranulosis is seen. Elongated and ectatic vessels of the dermis reach the top of the papilla and, together with the suprapapillary epidermal atrophy, explain why the curettage of scale produces bleeding (Auspitz sign). The perivascular inflammatory infiltrate is mild and when neutrophil exocytosis exists, intraepidermal pustules (Kogoj) or microabscesses in the horny layer (Munro) can be seen.

The initial lesion may not show the classic histopathologic features of the disease and, therefore, may not help in the diagnosis. Early papules can show slightly acanthotic epidermis with a mild infiltrate, without neutrophils. Parakeratosis is not a feature, and the presence of mast cell degranulation may be a clue for the diagnosis of eruptive lesions (guttate psoriasis). Examination of the border of expanding papules and plaques

shows suprapapillary edema and vascular tortuosity, and a mild perivascular inflammatory infiltrate is seen. Acanthosis and spongiosis may coexist, and the exocytosis of neutrophils can lead to the formation of the spongiform pustule of Kogoj in the epidermis. The further progression of this collection of neutrophils through the epidermis may lead to the accumulation of cells in the horny layer and the formation of Munro microabscesses. A more exuberant picture of neutrophil exocytosis and accumulation is seen in pustular variants [27].

Differential Diagnosis

Diseases that may develop erythematous and scaling lesions, with or without pustules, are among those that can mimic psoriasis in its wide range of forms. The concurrence of lesion in classic sites (extensor aspects of joints, scalp, navel, genitals), lesions on the nails and a positive familial history of psoriasis is frequently enough to confirm the diagnosis of psoriasis. Guttate psoriasis can be confounded with syphilis, and a serologic examination is mandatory. Pustular drug reactions can develop the same features as seen in generalized pustular psoriasis (von Zumbusch's) and the history of the disease is important in deducing a causal relation between drug intake and the development of lesions. Histologic examination in this case may be of lesser value as both diseases have similar features, with the exception of the occurrence of eosinophils in the examination, which may favor the diagnosis of pustular drug eruption. Palmoplantar keratoderma, hand eczema, and pompholyx are also differential diagnoses of psoriasis of palms and soles. The most common differential diagnoses are as follows [7, 19].

– *Atopic dermatitis:* Scaling in atopic dermatitis is less prominent and the affected sites are usually the opposite of those seen in psoriasis (flexural aspects instead of extensor aspects). Pruritus is variable in psoriasis and almost a rule in atopic dermatitis.
– *Seborrheic dermatitis:* Sometimes indistinguishable from mild psoriasis, especially in the face and scalp, sometimes leading to confirmatory skin biopsy. Scales tend to be smaller and not as flaky as in psoriasis, and severe infiltration is seldom seen in seborrheic dermatitis.
– *Cutaneous T-cell lymphoma (CTCL):* Sometimes a disease leading to erythroderma, CTCL can mimic psoriasis. Localized forms can be distinguished from psoriasis by lack of the coarse desquamation, seen in psoriasis, and by superficial atrophy with skin wrinkling seen in CTCL. In case of erythroderma, biopsy is required, as are laboratory examinations for *Sézary syndrome.*
– *Squamous cell carcinoma:* Can be suspected if there is only one or a limited number of treatment-resistant lesions, limited to sun-exposed areas.
– *Tinea:* Usually a cause of confusion with psoriasis if it occurs in palms and soles or flexural sites. KOH examination is needed to confirm the diagnosis.
– *Pityriasis rubra pilaris (PRP):* Can be a cause of erythroderma, but may mislead the diagnosis even if with fewer lesions. The brownish/copperish hue, the areas of spared skin among lesions, and the fewer inflammatory features of palmoplantar lesions in PRP are often sufficient to distinguish it from psoriasis.

Therapeutic Approach

Psoriasis is a chronic disease and its treatment should involve a long-term commitment between doctor and patient, whereby it is important to treat both the physical and psychological impacts of the illness. The concept of quality of life is as important as the concept of "cure," and the impact of therapies over the patient's life should also be taken into account. As different patients with psoriasis showing the same features may respond differently to the same treatment offered, an individualized approach is generally used.

Psoriasis treatment has greatly evolved since the understanding of the immune nature of the disease. There are several treatment guidelines available, almost all with a concordance of opinion. Patients should be assessed for disease severity and extension, which is made using the PASI, BSA, or DLQI. If any of these scores are 10 or higher (PASI ≥10, BSA ≥10, DLQI ≥10), the patient has moderate to severe psoriasis and topical treatment should not be used as monotherapy. The treatment goal should be at least 75% of improvement over baseline PASI, but 50–75% improvements can be tolerated if the patient is satisfied with current therapy, which is measured buy a DLQI less than 5 (Fig. 19.10) [25].

There is almost general consensus among available guidelines [28] that mild disease is initially treated with topical therapy. Nonresponders may undergo phototherapy and, sometimes, systemic therapy. Moderately to severely affected patients should not use topical treatment as monotherapy, and phototherapy/photochemotherapy is a first option for those who have no contraindication. Systemic antipsoriatic therapy has greatly evolved since the introduction of biologics and small-molecule inhibitors, following the greater understanding of the pathophysiology of the disease. Psoriatic arthritis should be always referred to a rheumatologist, and initial therapy usually comprises disease modifying antirheumatic drugs (DMARDs), such as methotrexate or leflunomide, with or without nonsteroidal anti-inflammatory drugs. Nonresponders

Fig. 19.10 Treatment goals and strategy for changing therapeutics according to clinical response

should promptly use biologics, and anti-TNF drugs are first-line therapeutics [25].

Mild Psoriasis

Mild psoriasis can be treated with topical drugs, which include potent corticosteroids, vitamin D analogs, calcineurin inhibitors, topical retinoids, and tar/liquor carbonis detergens (LCD) formulations.

First-line therapy is the combination of a topical corticosteroid and a vitamin D analog, usually betamethasone propionate and calcipotriol. This can be used until lesions are cleared. Caution should be taken with extended application of the compound for more than 30 consecutive days, but continuous long-term safe treatments of 52 weeks have been published in trials. After clearance is achieved, corticosteroid can be tapered down and, sometimes, only calcipotriol monotherapy can be maintained. In the event that the combination therapy is insufficient to achieve resolution of plaques, betamethasone can be replaced by a more potent corticosteroid, such as clobetasol propionate or halobetasol propionate.

Calcineurin inhibitor cream and ointments are not properly absorbed by thick skin, and are therefore used mainly on the face and genitals, and in flexural psoriasis. At those sites, response is similar to that of topical corticosteroids but without the risk of atrophy. Irritation after application is the major side effect in some patients.

Topical retinoids are a second-line option, but their use is limited by local irritation, which also occurs with anthralin. Therefore they cannot be used in unstable, very inflammatory lesions. Anthralin can stain the skin and, as its use is complicated by the limited time of the exposure to the drug by the patient, must be used by patients who can effectively comply with it. Absorption into the skin for longer periods of time than prescribed can lead to extreme irritation.

Tar and salicylic acid compound are useful adjuvants, but are generally not sufficient to treat psoriasis as monotherapy. Tar, and to a lesser extent LCD, has a pungent odor, which can be unpleasant especially for women [7].
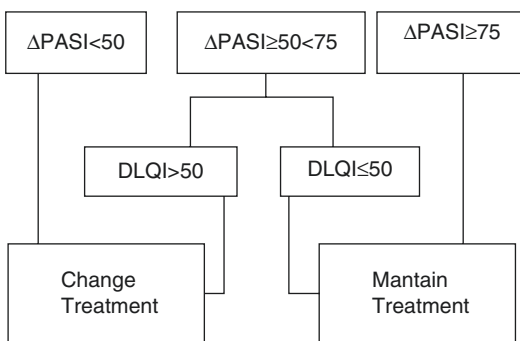
Phototherapy is also an option for patients who are not responsive or can no longer use corticosteroids because of side effects (most commonly atrophy) [25].

Moderate to Severe Psoriasis

Patients with moderate to severe psoriasis should no longer use topicals as monotherapy. After generalized disease is established, phototherapy/photochemotherapy is usually effective. Narrow-band ultraviolet B (UVB) without using oral drugs or UVA associated with the use of oral psoralens (PUVA) are both effective. Two to three sessions a week are needed for clearance and the amount of time per session is determined by testing the minimal erythemal dose. Some contraindications for phototherapy are current use of phototoxic drugs (e.g., hydrochlorothiazide), concomitant acquired or genetic photosensitive diseases or diseases prone to the development of skin cancers (e.g., lupus,), and history of worsening psoriasis with sun exposure and previous history of skin cancers (especially melanoma). Failure to achieve 50–75% improvement in the disease severity score (PASI, BSA, or DLQI) should prompt a treatment change [29].

Methotrexate is a potent inhibitor of the enzyme dihydrofolate reductase and is similar in its structure to folic acid. As it binds with great affinity to the enzyme of which folic acid is substrate, it prevents folic acid from mediating the conversion of dihydrofolate reductase to tetrahydrofolate. As tetrahydrofolate is necessary for the synthesis of purine nucleotides, methotrexate acts by inhibiting cell division (S phase). In psoriasis, the effect of methotrexate is achieved by immunosuppression rather than by inhibiting keratinocyte proliferation, inhibiting DNA synthesis in immunologically competent cells. Metabolism is hepatic but excretion is made through the kidneys. It can be administered orally, subcutaneously, and intravenously. It is available in 2.5-mg tablets or in 2-ml vials with a concentration of 50 mg/2 ml or 25 mg/ml [30]. Usual antipsoriatic doses ranges from 7.5 to 30 mg per week, and can be administered as a single oral or subcutaneous dose or as three divided oral doses over a 24-h period. Oral administration of methotrexate achieves a plateau of absorption after intake of 15 mg. Therefore, if higher doses are needed the subcutaneous route is preferable. Controversy still endures about the need of a lower test dose to access possible myelosuppression. Acute myelosuppression is rare, but a blood count should be taken after 1–2 weeks of treatment to evaluate its possibility. Folic acid supplementation is mandatory (1 mg/day).

Leucovorin is an antagonist of methotrexate and should be administered in cases of suspected toxicity. Long-term liver fibrosis is an adverse event of the chronic use of this drug whose occurrence can be diminished by lowering the methotrexate dose to a minimum of 2.5 mg after clinical response is obtained, by sequential liver tests (every 3 months in stable chronic users), and by accessing liver fibrosis after 4 g of cumulative dosage (fibroscan/liver biopsy) [25, 30].

Acitretin is a systemic retinoid, a vitamin A analog that has antiproliferative effects over the epidermis. It acts directly on gene transcription after binding to nuclear retinoid receptors. Immunomodulatory effects are known but are not of great importance in the psoriatic inflammatory cascade. Acitretin is teratogenic and should not be used in women of childbearing age. It is available in 10-mg and 25-mg tablets and usual doses for psoriasis range from 25 to 50 mg/day, but doses higher than 35 mg are restricted by side effects, generally xerosis and elevation of blood lipids [31].

Cyclosporine is a potent immunosuppressive agent found on a soil fungus (*Tolypocladium inflatum* Gams), and its effect on psoriasis was discovered after treatment of rheumatoid arthritis and psoriatic arthritis patients whose psoriasis lesions cleared after intake of the drug [32]. Although its mechanism is still not completely understood, its action in inhibiting the enzyme calcineurin leads to inactivation of T cells, mainly due to decreased IL-2 secretion. Cyclosporine is used today in a microemulsion form, and capsules are available in 25 and 100 mg and also in a 100-mg/ml solution. It is not cytotoxic or terato-

genic, and does not cause myelosuppression. Usual doses range from 2.5 to 5 mg/kg. There are two approaches when prescribing cyclosporine in psoriasis: one starting with a lower dose of 2.5 or 3 mg/kg and increasing the dose for optimal results if necessary, and the other starting with a higher dose of 4–5 mg/kg and decreasing the dose as soon as optimal results are achieved. Because of potential severe long-term side effects (nephrotoxicity, malignancies), the drug is reserved for severe recalcitrant psoriatic patients who had failed or had contraindications/reactions to previous classic therapies, such as phototherapy/photochemotherapy, methotrexate, or acitretin, and its use should be on a short-interval basis (up to 16–20 weeks). It is very useful to rescue patients from a severe flare or when patients have to be promptly cleared of their lesions (surgery, social events), as cyclosporine exerts its effects within a few days or weeks [33]. Contraindications to cyclosporine are decreased renal function, uncontrolled hypertension, presence/history of malignancies, and hypersensitivity to the drug. A full laboratory workup should be made before initiating the drug, and sequential monitoring of the renal function is mandatory [31].

Anti-TNF-α drugs are molecules that block the cytokine and prevent its action on the psoriatic inflammatory pathway. They are highly efficacious both in psoriasis and psoriatic arthritis [34]. *Etanercept* is a fully human fusion protein that mimics the TNF-α natural receptor, binding to TNF α. It is used as 50-mg subcutaneous injections twice a week for 12 weeks and then lowered to 50 mg per week. As it is not a monoclonal antibody, antidrug antibody formation is rare [34, 35]. *Infliximab* is a chimeric (25% murine, 75% human) immunoglobulin (Ig)G1 monoclonal antibody that binds to both soluble and transmembrane TNF-α. It comes as a powder in 100-mg vials that must be reconstituted in sterile water. Induction dose is 5 mg/kg intravenously on weeks 0, 2, and 6 and then every 8 weeks. As it is an intravenous infusion it is administered in a clinic/hospital setting. Infusion must be slow, taking no less than 2 h to avoid reactions. As it is a chimeric drug, antidrug antibody formation is expected to be more common after infliximab

infusions, but the clinical relevance of development of antibodies is still under debate [34, 36]. *Adalimumab* is a fully human IgG1 monoclonal antibody that binds to TNF-α and prevents it interacting with its natural cell surface receptor. In the presence of complement, it may lyse surface TNF-expressing cells. It is supplied in 40-mg prefilled syringe or pen, and dosage is 80 mg subcutaneously in week 0, 40 mg in week 1, then 40 mg every 2 weeks. Although it is fully human it may cause antidrug antibody formation, albeit low and of limited clinical relevance [34, 37].

Ustekinumab is a fully human monoclonal antibody IL-12/-23 inhibitor that binds to the p40 subunit shared by both cytokines and prevents Th1 and Th17 signaling, thus consequently altering the release and action of several other cytokines and chemokines (TNF-α, IFN-γ, IL-2, -6, -17, and -21). It is available in 45- or 90-mg prefilled syringes and doses are prescribed based on weight: 45 mg weeks 0 and 4 and then every 12 weeks if the patient weighs less than 100 kg, and 90 mg on the same administration scheme if patient is 100 kg or more. The same safety concerns used to establish a screening workup for TNF-α blockers are used for ustekinumab. One case of reversible posterior leukoencephalopathy syndrome (RPLS) was reported [34, 38].

Apremilast is a phosphodiesterase-4 inhibitor that blocks the conversion of cyclic adenosine monophosphate (cAMP) into AMP inside inflammatory cells. High intracellular levels of cAMP have an inhibitory effect on inflammation, downregulating the release of proinflammatory cytokines (TNF-α, IL-17, Il-23) and upregulating the release of anti-inflammatory cytokines (IL-10). It is available in 10- and 30-mg tablets and is administered orally, titrating the dose from 10 mg/day on day 1 to 60 mg/day on day 6 and after, with the aim of reducing gastrointestinal symptoms. Patients with severe renal impairment should use half the dose. Depression was reported in clinical trials, and caution is advised when used in patients with depression or a history of depression. Weight loss may be a side effect, and the use of apremilast together with rifampin, carbamazepine, phenytoin, or any CYP450 enzyme inducer may decrease the efficacy of apremilast [39].

Secukinumab is a fully human monoclonal IgG1 antibody that blocks IL-17A. IL-17 is a pivotal cytokine in psoriasis pathophysiology whose blockage results in downregulation of inflammation. Secukinumab is available in 150-mg prefilled syringes, pen, or lyophilized powder vial. The approved psoriasis dosage is 300 mg at weeks 0, 1, 2, 3, 4, and then every 4 weeks. A lower dose of 150 mg is sometimes acceptable for some patients. Screening and monitoring are the same as made for anti-TNF blockers and, as for all immunosuppressants, live vaccination should not be administered. Flares or even new cases of inflammatory bowel disease may happen after secukinumab treatment, and its use should be made with caution in patients with those conditions. It was recently approved for psoriasis by the FDA [40].

Glossary

Auspitz's sign Pinpoint bleeding following methodic curettage of the scales in a psoriatic lesion.

Clubbing Histopathologic term referring to elongated and widened rete ridges, which look like a club.

Erythroderma Scaling erythematous dermatitis that affects 90% or more of the body surface area. Psoriasis is one of the causes of erythroderma, but other diseases may also be causes.

Sézary syndrome A late stage of cutaneous T-cell lymphoma that is characterized by the epidermotropism of neoplastic CD4$^+$ T lymphocytes, which form microabscesses (Pautrier's microabscesses). Lymphadenopathy and presence of atypical T cells (Sézary cells) in the peripheral blood are signs of late-stage disease.

Tricophytoid lesion Lesion similar to a skin fungal infection (tinea). Its characteristic is a annular lesion with a more prominent border (active border), where the fungal activity resides.

von Zumbusch psoriasis Also called Von Zumbusch generalized pustular psoriasis, this is a severe and generalized form of pustular psoriasis. Pus consists of neutrophils. Drugs, emotional stress, infections, and sudden withdrawal of systemic steroids are some of the eliciting factors.

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Seborrheic Dermatitis

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Key Points

- Seborrheic dermatitis (SD) is a chronic inflammatory skin disorder and the affected areas are rich in sebaceous glands
- The prevalence of SD varies between 3% and 5%
- SD can cause visible scaling in hair and clothes, oily appearance, and foul odor. All these manifestations may be socially embarrassing, especially because they can be judged as poor hygiene
- Pruritus, scaling, facial erythema, odor, and the absence of a cure are the reasons for a decrease in the quality of life.
- Treatments include eradication of fungi, attenuation of the inflammatory process, and reduction of the sebum production.

Introduction

Seborrheic dermatitis (SD) is an inflammatory skin disorder, with a predilection for skin rich in sebaceous glands, affecting 3–5% of the population. It presents poorly demarcated red patches and greasy scaling on the scalp, face, upper aspect of the trunk, flexures, and groin. SD is an easily recognizable chronic dermatosis [1]. It affects infants and adults, often being associated with increased sebum production by the skin. The affected skin presents as erythematous, edematous, and covered with scales (or even crusts) that are yellowish, erythematous, or brown. SD ranges from mild to severe, including psoriasiform and erythrodermic forms. Pityriasis capitis (PC), or dandruff, is the denomination for mild cases without erythema and with reduced and dry scaling on the scalp.

SD and PC are characterized by epidermal hyperproliferation, increased intercellular and intracellular lipids, corneum envelope interdigitation, and parakeratosis [2]. SD can cause pruritus, and secondary infections occur occasionally.

A variety of treatment modalities is available, including eradication of fungi, reduction or attenuation of the inflammatory process, and decreased production of sebum [3]. Regarding the costs imposed by this cutaneous affection on public health, it is estimated that in the United States the annual direct, indirect, and intangible costs (from SD alone, excluding PC cases)

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achieve the total sum of US$1.2 billion. Furthermore, studies using quality of life assessment questionnaires have shown that the impact of SD is considerable [4]. The absence of a cure and the scant knowledge of its pathogenesis, in addition to the symptoms, substantiate these findings.

Epidemiology

SD is often described as common in adolescents and young adults. In patients older than 50 years, SD once again becomes frequent [5, 6]. The clinically significant estimated prevalence is 1–3% in young adults in the United States [7]. In a study conducted from 1971 to 1974 involving a representative sample of people from 1 to 74 years old in the United States population (through the National Health and Nutrition Examination Survey), the prevalence of SD, determined by dermatologists, was 11.6% on the whole. Cases in which the need for medical consultation was considered have been estimated at 2.8% (2.6% for men and 3% for women). In that sample the prevalence of SD needing medical consultation was lower in children under 12 years of age (less than 1%) and higher among people between 35 and 44 years (4.1%) [8]. This work, which was the most representative population study, demonstrated that SD is not rare in middle age, as described in many articles. When PC (dandruff) was considered, the observed prevalence exceeded 50% [9].

While SD was reported as rare among black persons [10, 11], it has also been described as common in black West Africans [12], although these data are contradictory. Prevalence of SD becomes quite high in patients with acquired immunodeficiency syndrome (AIDS), ranging from 30% to 80% [13–15].

Etiopathogenesis

Many theories exist regarding the etiology of SD, which remains controversial. Seborrhea or excessive sebum production is known as a predisposing factor for SD, but it is not detected in all affected patients [16].

Sebum is involved in epidermal structure development and in the maintenance of the epidermal permeability barrier [17], transport of antioxidants to the skin surface [18], protection against microbial colonization, and generation of body odor and pheromones [5]. Sebum has more recently been linked to specific hormonal signaling of the skin, epidermal differentiation, and skin protection against ultraviolet radiation [19, 20].

When secreted, sebum consists of triglycerides and esters, which are broken down by microbes into diglycerides, monoglycerides, and free fatty acids. Free fatty acids play an essential role in the early irritative response that triggers SD. The role of sebum secretion is also seen in the impact of stress and hormones on SD. These are known as factors that affect sebaceous secretion and thus cause SD to worsen [2].

SD in adults tends to appear during puberty, with the increase in cutaneous lipids that occurs during this period. The areas affected by SD are also rich in sebum production; furthermore, factors that increase seborrhea are associated with worsening SD. However, although SD occurs on the oily areas of the skin, we cannot consider seborrhea as the only cause of the disease. Many people have significant skin oiliness without the development of SD, and a study has shown that the rate of sebum production in the skin of individuals affected by SD was the same as in controls without the disease [16]. Another study examining the lipid contents of the forehead skin of 30 patients with SD and of 60 controls found a higher lipid content in SD patients compared with controls ($P = 0.0001$) [21]. Although few studies lead in this direction, and armed with only these data we cannot make a definite conclusion, the second study is methodologically superior and is more consistent with current knowledge about the disease.

Sebaceous gland function is responsive to stimulation by sex hormones and adrenal corticosteroids. Recent data demonstrated that skin treated with α-bungarotoxin, an acetylcholine receptor antagonist, markedly decreased sebum

production and pore sizes, suggesting that local neuronal stimulation may regulate sebaceous function [22]. The amount of sebum excretion has a bimodal distribution: it is high in the neonatal period under the influence of maternal sex hormones and then it rapidly decreases in childhood, correlating with the high prevalence of atopic dermatitis in this age group. Sebum secretion rate increases throughout the teens, and remains steady until its decline in both genders, although sebum excretion remains higher in males. These physiologic changes correlate with the timeline of how children "grow out" of their childhood atopic dermatitis, and the aging adult develops xerotic dermatitis.

A study assessed the link between the sebaceous glands and *Malassezia* [23]. There was an increase in the synthesis of neutral lipids in the presence of extracts of *Malassezia globosa* and *Malassezia restricta*. In this same study, the interleukin (IL)-8 production by human keratinocytes exposed to *Malassezia* extracts increased significantly compared with controls. In particular, two species, *M. globosa* and *M. restricta*, exerted a significant increase in IL-8, and of the two organisms *M. globosa* showed a significant effect.

The oral administration of isotretinoin, commonly used to treat acne, also reduces SD [24]. Since isotretinoin acts mainly by reducing the sebum production rate, it is thought that in this way it controls SD. However, isotretinoin also reduces epidermal proliferation, and this mechanism may also influence the improvement of SD (because in SD there is epidermal proliferation).

Some authors suggest hyperproliferation of the epidermis as another causal factor [25]. It has been proposed that the inflammatory process in SD causes an increase in turnover of keratinocytes and an incorrect maturation of the stratum corneum, resulting in a malfunction of the epidermal barrier [26].

SD was reported in a patient in whom seborrhea and unilateral SD developed on the face after facial nerve paralysis [27], and also in patients with torso paralysis [28]. These reports suggest that the paralysis could also be a triggering factor for SD. The reason why paralysis might have association with SD would be the faulty drainage of the pilosebaceous canal sebum. Such drainage, induced by skin movement, would occur in persons not affected by paralysis.

Another factor that can influence SD is the fungus of the genus *Malassezia* [29]. Although this genus of fungus is a member of the normal skin flora, it has been known to play roles in human diseases, such as PC, SD, pityriasis versicolor, and folliculitis caused by *Malassezia*. It could also cause exacerbation in atopic dermatitis and psoriasis [25, 30]. This fungus is common in areas rich in sebum.

Sebum secretion in human skin is a mixture of triglycerides, fatty acids, wax esters, steroid esters, cholesterol, cholesterol esters, and squalene [31]. When secreted, sebum consists primarily of triglycerides and esters, which are broken down by commensal microbes in diglycerides, monoglycerides, and free fatty acids. Human sebum contains saturated and unsaturated fatty acids, with a preponderance of the unsaturated.

The role of specific fatty acids becomes apparent when we examine the metabolism of *Malassezia. Malassezia* lipases and phosphatases hydrolyze sebaceous lipids, resulting in decreased triglycerides and a corresponding increase in free fatty acid by-products. *Malassezia* uses saturated fatty acid, leaving behind irritating unsaturated fatty acid such as oleic acid. These fatty acids can cause skin inflammation. To demonstrate that fatty acids produced by *Malassezia* can induce scaling in the human scalp, researchers applied a marked fatty acid (oleic acid) to the human scalp. Even when *Malassezia* was removed from the product containing oleic fatty acid produced by it, the product still prompted reaction with scalp scaling in susceptible individuals [31].

However, the same authors have shown that the use of oleic acid produced by *Malassezia* did not induce scaling in individuals not susceptible to PC or SD. Such a finding provides evidence of the role of these fatty acid metabolites in the development of scaling and suggests underlying differences among some individuals predisposed to develop PC or SD. An individual's sensitivity to the irritating free fatty acid penetration and the

resultant inflammatory response ultimately determines one's susceptibility for SD development.

Immunodeficiencies such as AIDS allow excessive proliferation of *Malassezia*, resulting in serious and extensive SD. Furthermore, some of the histologic features of SD have been reproduced by the inoculation of dead *Malassezia* in animal skin [32]. The wide variety of cytokines expressed in inflammation is similar to those seen in other fungal infections [33].

The difference between susceptible and nonsusceptible individuals remains unclear. Multiple possibilities exist, including innate differences in the barrier function of the stratum corneum, skin permeability, and immune response to free fatty acids or proteins and polysaccharides of *Malassezia* [9]. Subsequent studies are needed for us to understand comprehensively the susceptibility to SD.

Lipases may play a role in the life course of the species of *Malassezia* on the skin. For a better understanding of this role, one research group isolated the lipase of *Malassezia globosa* [34]. The protein was sequenced and the gene corresponding to the lipase (LIP1) was cloned and sequenced. This work was a first step toward the molecular description of lipid metabolism in the scalp and a better understanding of the role of microbial metabolism in the etiology of SD and PC. Based on the limited activity of LIP1, the authors concluded that *Malassezia* probably has other lipases, and that more studies are needed to delineate the complete metabolic pathway.

The genome of the most prevalent *Malassezia* in SD and PC has been completely sequenced. The *M. globosa* genome is 9 Mb, the smallest of any known free-living fungi [35, 36]. For proper identification of genes, the prediction of the protein-coding structures has been enhanced by the transcript sequencing of mRNA, allowing the prediction of 4289 protein-coding genes. Despite the small number of genes, the genome encodes the metabolic components for glycolysis, the tricarboxylic acid cycle, and the synthesis of all 20 canonical amino acids and of 5 bases of nucleic acids, probably revealing that most of the species of *Malassezia* are dependent on fatty acids for growth. In contrast to *M. globosa*, the genomes available to all other free-living fungi contain fatty acid synthases.

The necessity by *Malassezia* of assimilating external fatty acids is also reflected in the number of multiple lipases and phospholipases secreted (13 and 9, respectively). Reverse transcription–polymerase chain reaction (PCR) and proteomic experiments confirmed the expression of multiple lipase and phospholipase genes on human scalp.

The enzymes would need, therefore, to be in the extracellular environment to interact with the host's sources. Proteomic experiments were thus performed to identify more than 50 secreted proteins [9]. Some of the most abundant secreted proteins were, as hypothesized, lipases. In addition, many other secreted proteins have been identified, including aspartyl proteases, family members of phospholipase C, glucose-methanolcholine oxidoreductases (known as *Malassezia* allergens) [37], cell wall-modifying enzymes, and unknown proteins. Because these proteins are secreted, they would be more likely to interact with the skin and then mediate the pathogenicity of *Malassezia*, and could be therapeutic targets.

The lipid layer of *Malassezia* might also modulate the production of proinflammatory cytokines by keratinocytes [38].

Besides SD, *Malassezia* has also been associated with PC. This kind of fungus needs lipids for in vitro growth, corroborating its occurrence in humans in areas with increased production of sebum [39].

A 2008 study detected with PCR that the species of *Malassezia* most frequent in SD is *restricta*. However, the author himself concludes that we cannot yet determine if this fungus is pathogenic or not [29]. Another study found a higher prevalence of *Malassezia* (82%) in control patients than in patients with SD (76%) [40]. Bergbrant examined 30 people with SD and 60 controls, finding no significant differences in the average number of organisms (*Malassezia*) for both groups of patients [21]. However, Tajima has found in skin affected by SD a population of *Malassezia* three times higher than in unaffected skin in 31 patients with SD [29]. *M. restricta* and *M. globosa* were predominant among the species, comprising

93.5% and 61.5% respectively. Although Tajima has found a larger population of *Malassezia* in the affected skin compared with the unaffected, the study was conducted comparing them only in affected patients. The other studies, with a control group, found no difference or found greater populations of *Malassezia* in controls.

An important piece of evidence is that antiseborrheic shampoos (also called anti-dandruff) containing active agents against *Malassezia* are effective in SD [1, 41–43]. Improved scaling after treatment is accompanied by a reduction in the levels of *Malassezia* on the scalp [9]. Furthermore, the recolonization of *Malassezia* in SD recurrences corroborates its role [44]. With regard to improvement with systemic antifungal agents, since they have anti-inflammatory effects associated with antifungal effects, it cannot be said that the fungi are the only factors in SD. The data concerning the role of *Malassezia* in SD are still controversial. Piérard claims that diseases in which *Malassezia* is involved are caused by a lack of control of natural innate antimicrobial defense mechanisms [45]. He argues that the simple skin contamination by *Malassezia* spp. commensal does not induce a clinically relevant response of the host. Thus the corneocytes, or only a few of them, could play this role in inflammatory diseases caused by *Malassezia*. Individuals predisposed to PC and SD would be those who do not respond adequately to the presence of *Malassezia.* Thus, the epidermal cells could fail to express the skin's defense mechanisms. In response to the secondary accumulation of fungi, there would be an inflammatory reaction ranging from mild to severe [46]. Consequently, as in most inflammatory skin diseases, scaling of corneocytes would then be altered, with the occurrence of a scaly aspect. The most likely and accepted fact is that SD is an association between fungal infection of the genus *Malassezia*, seborrhea, and individual sensitivity [47].

Also regarding the immunologic hypothesis, theories based on SD immunologic studies propose that the disease's pathogenesis is due to an inadequate immune response of the host to the fungus, the toxins produced by the fungus, or irritants produced by the fungus. Epidemiologic data showing a higher prevalence of SD in immuno-compromised individuals (previously mentioned in the text) suggest that the disease is due to an inadequate immune response to *Malassezia*. However, Perry and Sharpe have refuted such an idea by quantifying antibody production in response to *Malassezia* antigens in 19 patients with SD, as well as the cellular immune response to *Malassezia* antigens in 16 patients with SD [48]. The comparison of these data with those of healthy controls matched for age and sex found no significant differences, suggesting that SD is not the result of an increased or decreased immune response to fungi.

Another study compared the *Malassezia* cultures of 28 human immunodeficiency virus (HIV)-positive individuals (including 7 with SD) with a control group of 20 HIV-negative individuals (including 10 with SD) [49]. Results of the cultures of HIV-positive individuals with SD clinical signs demonstrated a very small or missing content of fungi, while the results of HIV-negative individuals with SD exhibited significantly higher content of *Malassezia*. These findings suggest that SD in HIV-positive persons may suffer a distinct pathogenic mechanism in relation to classic SD in immunocompetent individuals. However, such data come from a study with a very limited number of patients.

Prohic found no differences in the distribution of species of *Malassezia* in SD lesions among immunocompetent and immunocompromised individuals [50]. However, the larger amount of positive cultures in immunocompromised patients would confirm that cellular immunity could facilitate the survival of skin fungi.

In an in situ study of inflammatory cells and mediators in SD patients' skin, an increase was found in nonimmunogenic stimuli such as neurokinin-1, CD16+, and complement [33]. These data suggest that irritative products produced by *Malassezia* can cause a rise in the response activated by the complement. There is also an increased level of inflammatory interleukins and lymphocyte-stimulating interleukins T helper-1 (Th1) and Th2 in both the affected skin and the skin not affected by SD, possibly due to stimulation of the immune host system by *Malassezia*.

Authors have proposed that fungi of the genus *Malassezia* could induce an inflammatory reaction, producing toxic mediators released only under specific growing conditions [48]. The unpredictable course of SD could be explained by this theory. Studies on fungi of the dermatophyte class have identified a liposoluble molecule that features the function to mediate chemotaxis of neutrophils and induce inflammatory reactions in the host [51]. The researchers named this substance chemotaxin lipid-like leukocyte activator (LILA). Cross-sensitization experiments have shown that several species of fungi can produce LILA or structural variants of it, representing a signal to the host's phagocyte system similar to the N-formylated methinyl peptides in bacterial infections. In addition to the possible inflammatory response induced by LILA, the lipase activity of *Malassezia* produces irritating fatty acids and arachidonic acids, which can also contribute to the inflammatory reaction of SD [52].

In the past there were only few reports regarding SD susceptibility and human leukocyte antigen (HLA). All were carried out in the 1970s and reported A30 and/or A31 and B12 (corresponding to HLA-B*44 or HLA-B*45) association. However, a recent study added the alleles A*32 for class I and DQB1*05 and DRB1*01 for class II [53].

Associated Factors

Hormones

The hypothesis of a relationship between SD and hormones would make sense because the condition appears in infants (by the transfer of maternal hormones), disappears spontaneously with the elimination of these hormones (up to 12 months of age), and reappears more prominently at puberty [1]. However, it does not explain why it reappears after the age of 50 years (at which stage the hormones are declining).

Sex

In the study by Gupta et al. [54], the predominant sex in patients with SD was male. These results were attributed to a stronger action of androgens on the pilosebaceous unit in males. The largest study, however, from which to draw conclusions on the influence of sex on SD would be NHANES, previously described, in which cases with a considered need for medical consultation were estimated at 2.8% (2.6% for men and 3% for women).

Body Fat, Body Mass Index (BMI), and Hypertension

A study by the authors of this chapter, involving 2201 patients, has found an association between scalp SD and increased body fat (confirmed by tricipital skin folds and BMI) [55]. The BMI data are only in the doctoral thesis [56], while the article has described the relationship with tricipital skin folds. The mechanisms involved in this association are not known. Obesity is related to insulin resistance, but a study did not find high levels of insulin associated with scalp SD [57]. However, obesity can lead to hyperandrogenism and elevation of testosterone levels, which could account for the increase in seborrhea [58, 59]. Data demonstrating the effect of antiandrogens on seborrhea treatment support the role of hyperandrogenism in SD.

Treatment of women with oral contraceptives containing antiandrogenic properties led to improvement or resolution of seborrhea [60, 61]. Another observation is that the use of anabolic steroids by competitive sports practitioners can cause SD [62]. The mechanism proposed was sebaceous gland hypertrophy, resulting in increased sebum production.

Two studies, each comprising more than 2000 teenagers or young adults, found no association between acne and SD [55, 63].

Besides being associated with an increase in body fat, a recent study of 9255 patients found an

association between SD and hypertension in adults [64], further corroborating inflammatory dermatoses such as SD and metabolic syndrome.

Emotional Stress

As a triggering factor, emotional stress has always been considered by individual clinical observations, but there is little scientific evidence corroborating such data. In a small study of SD patients emotional stress was associated with the triggering or relapse of SD [65]. This study was conducted in two phases. The first phase collected, by a questionnaire, individual data such as psychiatric history, SD characteristics, and identity. Information about SD triggering factors was obtained through an open questionnaire. The patients were then questioned about psychological stress during the week or month preceding the active episode.

A second questionnaire containing the same questions was applied 4 months later. The two questionnaires contained psychopathologic evaluation scales designed to detect symptoms of anxiety and depression (HAD: Hospital Anxiety and Depression scale; Beck; STAI: State-Trait Anxiety Inventory) and determine the perceived stress (PSS: Perceived Stress Scale). SD was linked to stress and anxiety, but not to depression. However, patients with SD on the face were more depressed (Beck scale).

Sun Exposure

In adolescents and adults with chronic SD, there is a worsening during the winter period. However, the effect of solar radiation is still unclear. Although there is some evidence that sun exposure can improve the clinical appearance of SD [66], it has also been reported that some people may develop SD when subjected to phototherapy with psoralen and ultraviolet A radiation (PUVA) [67]. PUVA-induced SD can be prevented by covering the face during irradiation.

More evidence that solar radiation would not have a beneficial effect on SD comes from the fact that there is a high prevalence of SD among mountain guides, who are constantly subjected to sunlight [68].

Medications

Medications, abnormalities in neurotransmitters, physical factors, nutritional disorders, genetic factors, and immunodeficiencies all have possible association with SD [54].

Drugs that might exacerbate or trigger SD include haloperidol, lithium, buspirone, chlorpromazine, auranofin, cimetidine, ethionamide, gold, griseofulvin, interferon-α, methyldopa, phenothiazines, psoralens, stanozolol, and thiothixene [3, 69, 70].

Neurogenic Theory and Parkinson's Disease

A neurogenic theory for the development of SD exists due to its association with parkinsonism and other neurologic disorders, including cerebrovascular accidents, epilepsy, head trauma, facial nerve paralysis, and syringomyelia induced by neuroleptic drugs with extrapyramidal effects [71]. The prevalence of SD in Parkinson's disease patients ranges from 52% to 59% [72]. Parkinson's disease patients, when treated with L-dopa, undergo remission in SD [73]. Although associations with neurologic diseases are well established, they represent a minute proportion of SD cases.

There are three theories regarding the association between SD and Parkinson's disease [74]. The first, one of the most supported theories, states that a depletion of dopamine in Parkinson's disease leads to a decrease in release of endocrine factors, especially the melanocyte-stimulating hormone (MSH), which would increase sebum production and cutaneous manifestations typical of SD. The effects of dopaminergic agents have

been studied in parkinsonian patients, resulting in findings of a reduction in sebum production.

Another hypothesis is that the stiffness and amimia of parkinsonian patients could give rise to an increase in the static pool of secreted sebum and thereby support the growth of *Malassezia* yeasts, with ensuing emergence of SD. Treatment with levodopa would be beneficial for recovering skin mobility and therefore eliminating accumulated sebum in the pilosebaceous canal.

The third hypothesis states that SD would be the cause of Parkinson's disease, and not the opposite. This is the least accepted hypothesis and the one that makes least sense.

AIDS

SD is also one of the most common cutaneous manifestations in patients with HIV, being more serious and prevalent in these patients [13]. SD incidence ranges from 30% to 83% in this group [15]. In these patients a greater body length is affected, especially when CD4 numbers fewer than 400 cells per mm^3 [75]. There may be sudden onset in patients with HIV, a situation that should generate suspicion in the clinician. Remission is usual with antiretroviral therapy [13].

An increased risk of inflammatory dermatoses has been reported in patients positive for both HIV and human T-lymphotropic virus 1, indicating possible importance of this group of infections in the development or worsening of certain dermatologic diseases [76, 77].

There are also sporadic reports and small studies linking other conditions to SD, such as familial amyloidosis and chromosome 21 trisomy [78, 79].

Skin Color

SD is described as rare in persons with black skin [10, 11]. In such cases, HIV infection should be suspected. However, SD was also described as common in black Africans from the West [12]. The data are contradictory, and few studies

evaluate this aspect in a methodologically correct way. Perhaps SD is underdiagnosed because of the fact that in some black patients SD presents itself only as hypochromia in the affected areas of the face. In addition, the SD erythema may be less visible in people with darker skin.

Quality of Life

SD in adults is very prevalent, chronic, and often uncomfortable, causing pruritus, bad aspect, and unpleasant odor, especially in the face and scalp [25]. Improvement in the quality of life of patients is possible if effective treatment of is carried out [80].

Clinical Presentation

SD commonly affects young adults, adolescents, and infants (Table 20.1). In the case of infantile SD, eruption begins in the period between 2 weeks and 6 months of life. It affects up to 70% of infants in the first months of life, but disappears until 12 months [81]. It may start on the scalp or in the diaper area. Later the skin folds, face, and trunk may be affected. The rash com-

Table 20.1 Clinical forms of SD

Infantile	Begins between 2 weeks and 6 months of life
	Affects up to 70% of infants in the first months of life
	Disappears until 12 months
	Usually starts on the scalp or diaper area
	May evolve to skin folds, face, and trunk
	The rash comprises well-defined areas of erythema and scaling
	Usually more intense on the scalp
Adolescents and adults	Mainly the scalp
	Can also affect the forehead, eyebrows, eyelids, nasolabial folds, chin, ears, central chest, and interscapular areas
	More than 50% of the adults are affected by dandruff (PC). Between 3% and 5% of adults are affected by SD that requires a medical consultation

Fig. 20.1 Auricular SD
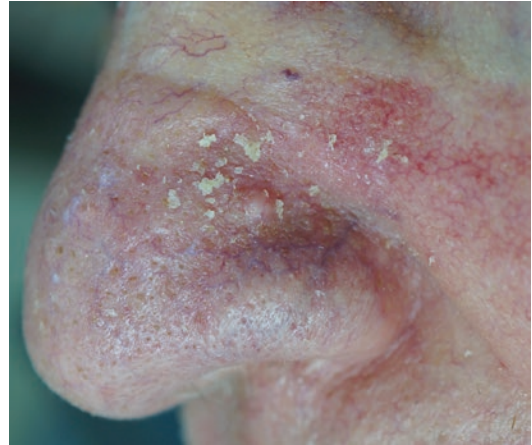
Fig. 20.3 Marked desquamation and inflamation in SD of the nose

Fig. 20.2 Glabela, eyebrows and forehead with mild SD

Fig. 20.4 Mild desquamation and erythema in the medial eyebrow

prises well-defined areas of erythema and scaling. It is usually more intense on the scalp. On the skin folds there is often an intense erythema. The scales are rather adherent; they are yellow-brown in color, large and greasy in the scalp, but smaller, whiter, and drier in other areas.

In adolescents and adults, SD affects mainly the scalp but can also affect the forehead, eyebrows, eyelids, nasolabial folds, chin, ears, central chest, and interscapular areas (Figs. 20.1, 20.2, 20.3, 20.4, 20.5, 20.6, 20.7, 20.8, and 20.9). The region most affected by SD is the scalp, with

Fig. 20.5 Nasolabial fold and nose with SD
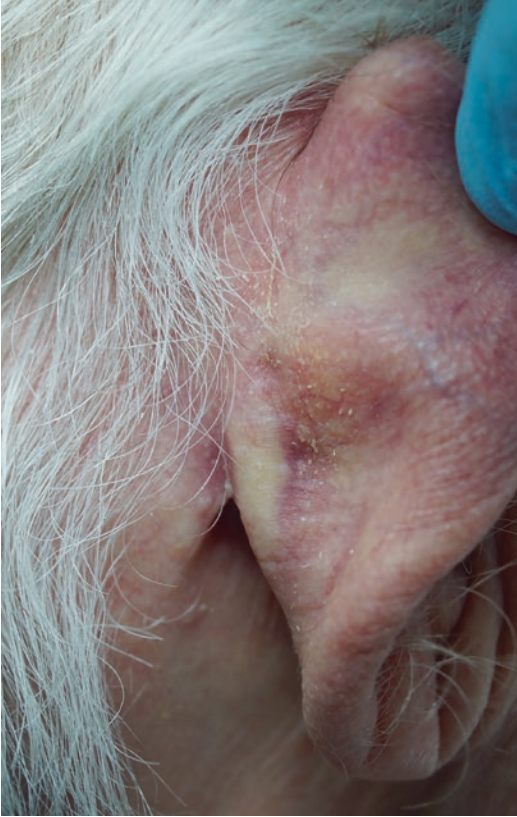
Fig. 20.6 Postauricular SD- a common affected area

Fig. 20.7 Intraauricular SD

the occurrence of erythema and scaling of vary-ing extent. When there is only peeling, without erythema, PC or dandruff is characterized [1]. Some authors believe that this may be the nonin-flammatory variant of SD [82]. Although there is no visible inflammation, only scaling, the inflam-matory process is present and is demonstrated in the histology. More than 50% of adults are affected by PC or SD, and the socioeconomic impact is very high [9].

SD can cause visible scaling in hair and clothes, oily appearance, and foul odor. All these manifestations may be socially embarrass-ing, especially because they can be judged as poor hygiene [75]. A study of 3000 patients with SD demonstrated, based on the Dermatology Life Quality Index (DLQI), that SD affects the quality of life of its carriers [4]. Pruritus, scaling,

facial erythema, odor, and the absence of a cure were the reasons for this decrease in the quality of life. PC carriers showed significantly better quality of life indices than individuals with SD (5.34 ± 4.67 points compared with 7.73 ± 5.3 points, respectively; $p < 0.001$).

The other areas where SD may occur (also characterized by erythema and scaling) are the nasolabial folds, the glabella, the eyebrows, the retroauricular regions, the external audi-tory canal, the mentum, the anterior chest, and the interscapular region [1]. In an unusual manifestation, it may occur on flexural areas or become widespread over the whole body or part of it [83].

Fig. 20.8 SD in the preauricular area

Fig. 20.9 Scalp SD

Table 20.2 Diagnosis

Clinical	Almost all cases
Dermoscopy	Mainly to differentiate from scalp psoriasis
Histology	Nondiagnostic in SD
	Could be useful to differentiate it from other diseases
	Depends on the clinical stage of the disease
Confocal microscopy	Could be used when there is need for biopsy but the patient does not accept it

(16/20, 80%), hairpin vessels (17/20, 85%), white scales (10/20, 50%), and punctate hemorrhages (12/20, 60%). By contrast, SD was characterized by arborizing vessels (16/20, 80%), atypical red vessels (13/20, 65%), featureless areas (20/20, 100%), and honeycomb pigment (9/20, 45%) [84].

Histology is nondiagnostic in SD, although it may be useful to differentiate it from other diseases. The histopathology of SD depends on the clinical stage of the disease [85]. In the acute and subacute phases, an inflammatory infiltrate composed principally of lymphocytes and histiocytes is found in association with mild to moderate spongiosis and psoriasiform hyperplasia combined with parakeratosis around follicular ostia ("shoulder parakeratosis"). During the chronic phase, in addition to the aforementioned findings, there is marked psoriasiform hyperplasia with dilatation of the capillaries and venules of the superficial plexus, which makes it very similar to psoriasis. In psoriasis vulgaris, the histopathologic findings are similar except for spongiosis.

For the less common cases, when there is need for biopsy but the patient does not accept it, confocal microscopy may be used if available. However, this remains an expensive method with limited availability. Agozzino has used confocal microscopy to differentiate SD from psoriasis on the face. He has found specific and easily recognizable confocal patterning in SD, supporting clinical differentiation with psoriasis [86].

Diagnosis: Dermoscopy, Confocal Microscopy, and Histology

The diagnosis of SD is essentially clinical, although dermoscopy can help in the differentiation of scalp SD and scalp psoriasis (Table 20.2). One study demonstrated that the most significant dermoscopic features of scalp psoriasis included dotted vessels (10/20, 50%), glomerular vessels (13/20, 65%), red loops

Differential Diagnosis

Among possible differential diagnoses are psoriasis, atopic and contact dermatitis, candidiasis, erythrasma, impetigo, rosacea, dermatophytosis, Langerhans cell histiocytosis, Wiskott–Aldrich syndrome, cutaneous lupus erythematosus, dermatomyositis, vitamin B deficiency, zinc deficiency, and drug eruption (Box 20.1). However, the diagnosis is clinical with strong emphasis on history and physical examination of the patient, being simple for the dermatologist [3, 87]. In children, however, SD may be mistaken for tinea capitis [3].

Box 20.1 Differential Diagnosis
Psoriasis
Atopic dermatitis
Contact dermatitis
Candidiasis
Erythrasma
Impetigo
Rosacea
Dermatophytosis
Langerhans cell histiocytosis
Wiskott–Aldrich syndrome
Cutaneous lupus erythematosus
Dermatomyositis
Vitamin B deficiency
Zinc deficiency
Drug eruption
Tinea capitis

Therapeutic Approach

Besides being very prevalent, SD is a chronic disease, and treatments are prolonged or continuous. There are different forms of treatment, including eradication of fungi, reduction or attenuation of the inflammatory process, and decrease of sebum production [3] (Box 20.2).

SD treatment is based mainly on topical antifungals. Among the most extensively studied agents are ketoconazole, bifonazole, and ciclopirox olamine, which are available in creams, gels, foams, and shampoos. Despite its activity against fungi, many of them also have anti-inflammatory activity. For example, certain antifungals (such as ketoconazole, itraconazole, and bifonazole) inhibit 5-lipoxygenase, which then blocks leukotriene B4 synthesis in the skin, causing reduction of inflammation [46]. Since such drugs have this effect, perhaps we cannot attribute the improvement only to the antifungal effect but to a combined effect. However, this weak anti-inflammatory effect alone would not be sufficient.

Propylene glycol (propane-1,2-diol) and other agents found in many topical therapies have potentially beneficial action mechanisms for SD [88]. This may be the explanation for the great improvement found in placebo groups [89].

In 2015 the Cochrane Collaboration conducted a review of studies with topical antifungals in SD [90]. Included were 12 ketoconazole trials ($N = 3253$), 11 ciclopirox trials ($N = 3029$), two lithium trials ($N = 141$), two bifonazole trials ($N = 136$), and one clotrimazole trial ($N = 126$) that compared the effectiveness of these treatments versus placebo or vehicle. Nine ketoconazole trials ($N = 632$) and one miconazole trial ($N = 47$) compared these treatments with steroids. Fourteen studies ($N = 1541$) compared one antifungal with another or compared different doses or schedules of administration of the same agent with one another.

Topical ketoconazole 2% treatment showed a 31% lower risk of failed clearance of rashes compared with placebo (risk ratio (RR) 0.69, 95% confidence interval (CI) 0.59–0.81, eight studies, low-quality evidence) at 4 weeks of follow-up, but the effect on side effects was uncertain because evidence was of very low quality (RR 0.97, 95% CI 0.58–1.64, six studies); heterogeneity between studies was substantial ($I^2 = 74\%$). The median proportion of those who did not have clearance in the placebo groups was 69%.

Ketoconazole treatment resulted in a remission rate similar to that of steroids (RR 1.17, 95% CI 0.95–1.44, six studies, low-quality evidence), but occurrence of side effects was 44% lower in the ketoconazole group than in the steroid group (RR 0.56, 95% CI 0.32–0.96, eight studies, moderate-quality evidence).

Ketoconazole yielded a remission failure rate similar to ciclopirox (RR 1.09, 95% CI 0.95–1.26, three studies, low-quality evidence). Most comparisons between ketoconazole and other antifungals were based on single studies that showed comparability of treatment effects. Ciclopirox 1% led to a lower failed remission rate than placebo at 4 weeks of follow-up (RR 0.79, 95% CI 0.67–0.94, eight studies, moderate-quality evidence) with similar rates of side effects (RR 0.9, 95% CI 0.72–1.11, four studies, moderate-quality evidence). Among other antifungals, clotrimazole and miconazole efficacies were comparable with those of steroids on short-term assessment in single studies. Treatment effects on individual symptoms were less clear and inconsistent, possibly because of difficulties encountered in measuring these symptoms. Evidence was insufficient to conclude that dose or mode of delivery influenced treatment outcome. Only one study reported on treatment compliance. No study assessed quality of life. One study assessed the maximum rash-free period but provided insufficient data for analysis. One small study in patients with HIV compared the effect of lithium versus placebo on SD of the face, but treatment outcomes were similar [91].

Intermittent use of shampoos containing ketoconazole can maintain the disease in remission. In one study, 312 patients with scalp SD (resolved with the use of ketoconazole shampoo 2% twice a week) were subsequently included in a placebo-controlled clinical trial for another 6 months. The relapse rates were 47% for patients using placebo, whereas patients using ketoconazole shampoo once every 2 weeks had relapses in 31% of cases, and only 19% had relapses with the use of ketoconazole shampoo once a week [92].

In the authors' experience, when the antifungal is not effective the most appropriate measure is to combine topical corticosteroids of low or medium potency with topical antifungal initially (instead of using isolated corticosteroid), keeping the antifungal as maintenance. There is a risk of atrophy and hypertrichosis when using topical corticosteroids for a chronic condition [87].

The use of shampoo containing selenium sulfide 2.5% for scalp SD was more effective than placebo but less so than the treatment with 2% ketoconazole shampoo [93]. Topical lithium succinate and gluconate have been more effective alternatives than placebo in SD treatment in areas other than the scalp, but less effective than ketoconazole [87, 91]. Lithium's mechanism of action is poorly understood.

The use of an antibiotic was also effective in SD treatment. Metronidazole gel proved to be as effective as ketoconazole cream in treatment of facial SD. However, this result was found in a small randomized double-blind study [94].

Most over-the-counter antiseborrheic shampoos have zinc pyrithione in its formulation, and are used in concentrations ranging from 1% to 2%. Its pharmacologic action seems to be fungistatic, antimicrobial, keratolytic, and sebum-reducing [46, 95, 96]. Randomized clinical trials have shown that its effectiveness in shampoos was lower than that of ketoconazole [46].

Another recent Cochrane review analyzed the anti-inflammatory treatments for SD of the face and scalp [97]. Thirty-one randomized clinical trials were found that examined topical steroids, seven that examined calcineurin inhibitors, and three that examined lithium salts. Overall, the median rate of achieving total clearance was 53% (13–100%) with anti-inflammatory treatments (topical steroids, calcineurin inhibitors, or lithium salts) across studies, and the median (range) rate of adverse effects was 7% (0–57%). The most commonly reported adverse effects were burning, pruritus, erythema, and dandruff.

In the short term (4 weeks) there were no statistically significant differences between steroid therapy and calcineurin inhibitor therapy in total clearance (relative risk (RR), 1.08; 95% CI, 0.88–1.32). Steroids and calcineurin inhibitors were comparable in all other outcomes as well. Adverse events were less common in the steroid group compared with the calcineurin inhibitors group in the short term (RR, 0.22; 95% CI, 0.05–0.89). Also in the short term, the rates of total clearance were comparable between the topical steroid and azole groups (RR, 1.11; 95% CI, 0.94–1.32), but there was less erythema and scaling associated with steroid use.

In general, mild and strong steroids had comparable therapeutic effects and adverse events, but total clearance took longer in the low-potency group. Treatment with lithium salts resulted in total clearance more often than treatment with azoles (RR, 1.79; 95% CI, 1.10–2.90, 4 weeks) but had similar rates of reported adverse effects.

Only minor differences in treatment effects among anti-inflammatory treatments were found. Strong steroids were more effective than azoles in reducing erythema, scaling, and pruritus, but both treatment modalities were comparable regarding safety profiles. The efficacy of steroids was also comparable to that of calcineurin inhibitors, but with fewer adverse effects. Mild and strong steroid compounds were comparable in achieving total clearance at short-term follow-up. No significant differences between calcineurin inhibitor and azole treatments in effectiveness or adverse effects were found. Lithium salts were more effective than azoles but had a similar frequency of adverse effects. On the basis of this review, there are no clear differences in treatment effects among the assessed treatment options.

Combination treatments with multiple different classes of topical therapies were not included. In general, the level of evidence was low to moderate according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.

In a 20-week, prospective, multicenter, comparative study conducted at nine centers in Korea, tacrolimus ointment twice a week was used to maintain remission in patients treated with tacrolimus ointment for up to 4 weeks [98]. A total of 27 SD patients (30.0%) experienced adverse events that were assessed by the investigators of this study. Burning sensations, erythema, folliculitis, and pruritus at application sites were common adverse events, some of which overlapped with each other. Among these, six SD patients requested to be withdrawn from the study because of adverse events. Fifty-four patients (65.0%) in the SD group had no disease exacerbation during the 20 weeks of treatment phase. In a previous study [99], a double-blind, vehicle-controlled, multicenter trial using 0.1% tacrolimus ointment in facial SD, all of the ten patients of the placebo group had disease exacerbation in 10 weeks. Eight patients of the placebo group had disease exacerbation at 2 weeks, one patient at 4 weeks, and the other patient at 6 weeks. This study was conducted with a total of 75 patients who had had their SD stabilized with a 2-week course of treatment using 0.1% tacrolimus. After stabilization, randomization was carried out in a double-blind fashion to treatment with 0.1% tacrolimus once a week, 0.1% tacrolimus twice a week, or vehicle twice a week, for 10 weeks (maintenance). Significant improvement in erythema, scaling, and pruritus compared with baseline was maintained during the maintenance phase in both tacrolimus groups, but not in the vehicle group. The mean recurrence rate according to global assessment was significantly higher in the tacrolimus once-weekly group than in the twice-weekly group. This study concluded that twice-weekly treatment with 0.1% tacrolimus ointment had superior effects in keeping facial SD in remission.

This remission maintenance therapy of skin diseases with twice-weekly tacrolimus ointment has already been used in atopic dermatitis and vitiligo with excellent results. Now, in this study, it showed similar outcomes in SD control.

However, in public health we have to take into account that topical tacrolimus is a high-cost medication. Since inexpensive medications such as topical ketoconazole have response rates similar to those of tacrolimus, we should consider primarily using these more cost-effective medications. As for maintaining remission, cheaper medications possibly also work well in most patients, although there are no studies with regard to SD of the face. Therefore we can, primarily, exercise maintenance with cheaper topical medications. There are excellent outcomes in the authors' experience with 2% ketoconazole cream once to seven times per week, according to the need (unpublished data). We usually start after the control of SD, with 2% ketoconazole three nights per week, subsequently increasing or decreasing the frequency according to control and tolerance. If there is no control, we then try the tacrolimus.

As the areas affected by SD are usually thin-skin areas such as the face and skin folds, we must be careful when using topical corticosteroids, even more so for a chronic condition whereby patients, on their own, can maintain the usage for long periods. Another interesting characteristic of tacrolimus for its use in SD is the fact that it has been found to be active against fungal strains, including *Malassezia furfur* and various other *Malassezia* strains that are closely related to the pathophysiology of SD.

A small randomized, placebo-controlled trial assessed oral itraconazole in SD treatment [100]. Sixty-eight patients with moderate to severe SD were randomly assigned to the itraconazole (*n* = 35) or placebo (*n* = 33) groups. Itraconazole 200 mg/daily or placebo was prescribed for 1 week and then for the first 2 days of every month for the following 3 months. Patients were followed for 4 months and the Seborrheic Dermatitis Area Severity Index (SDASI) was measured on nine anatomic sites. Statistically significant improvement was observed in SDASI of both itraconazole and placebo groups (*p* = 0.000), but the itraconazole group showed significantly higher efficacy compared with placebo (*p* = 0.023). Clinical improvements of 93.8%, 87.5%, and 93.1% were observed at the end of 2 weeks, 1 month, and 4 months, respectively, in the itraconazole group, and 82.1%, 64.3%, and 53.6% in the placebo group. Furthermore, the recurrence rate in the itraconazole group was significantly lower than in the placebo group (*p* = 0.003). No blood test abnormality was seen in any patient.

One study compared fluconazole and terbinafine in patients with moderate to severe SD [101]. Sixty-four patients with moderate to severe SD were enrolled in a randomized, parallel-group study. One study group took terbinafine 250 mg daily (*n* = 32) and the other fluconazole 300 mg (*n* = 32) weekly for 4 weeks. Terbinafine showed greater reduction in disease intensity.

Two randomized controlled trials assessed oral terbinafine, 250 mg daily, for 4–6 weeks, demonstrating superiority over the placebo group.

One randomized controlled trial assessed the use of ketoconazole, 200 mg/day, for 4 weeks or an unspecified duration. Significant improvement compared with placebo was seen in scalp scaling, scalp erythema, and SD scores at other sites.

Other open noncomparative trials assessed the systemic use of other antifungal agents, isotretinoin and prednisone, in SD, but the quality of evidence is too low [102].

Abraham et al. reported a case involving the successful treatment of SD with isotretinoin in a 42-year-old man [103]. The patient was previously unresponsive to oral and topical antibiotics/antifungal therapies. Treatment consisted of 20 mg daily of isotretinoin and topical ketoconazole for a period of 1 year. No relapse was noted. Although it is merely a case report, in patients who do not respond to all other possible therapies it may be the only alternative.

The problem of studies conducted with SD patients is that they are short-term. Since SD is a chronic condition, treatment will be long-term, and side effects should be considered in this context. Another concern with the short-term studies is their effectiveness in chronic use. Studies with larger numbers of participants would also be interesting to arrive at a better understanding of their real effectiveness.

Because short-term total clearance was achieved in only half of the patients with currently available agents, there is a need to identify more efficacious treatments or methods for designing innovative regimens that combine existing treatments. In practice, but not in the studies, this large number of patients who do not respond to treatment can be effectively managed with the combination of treatments (authors' experience, unpublished data). A commonly used treatment is the combination of a topical corticosteroid with an antifungal initially, keeping only the antifungal as maintenance. If there is no maintenance with the antifungal, one may use tacrolimus, systemic antifungals, or even oral isotretinoin.

The treatment of infantile SD consists primarily of emollients [104] that help loosen scales (e.g., olive oil, petroleum jelly). Scales can then

be removed by rubbing with a cloth or infant hair brush. One study showed that ketoconazole 1–2% cream is effective and seems to be safe when used twice daily for 2 weeks. There are no shampoos that have been approved by the US Food and Drug Administration for treatment of SD in children younger than 2 years of age. In the authors' experience, when there is significant associated inflammation, there is a need to use topical corticosteroids for a few days, keeping moisturizers and topical antifungals as maintenance when needed.

Box 20.2 Common Treatments for SD
Scalp:
Ketoconazole 2% shampoo daily initially, then twice per week
Selenium sulfide shampoo twice per week
Zinc pyrithione shampoo twice per week
Coal tar shampoo twice per week
Ciclopirox 1% shampoo daily until remission, then twice per week
Betamethasone valerate foam 0.12% twice daily
Clobetasol 0.05% shampoo twice weekly
Fluocinolone 0.01% shampoo daily
Fluocinolone 0.01% solution once or twice daily

Face and body:
Ciclopirox 0.77% gel or cream twice daily for up to 4 weeks
Ketoconazole 2% cream, foam or gel twice daily for 8 weeks, then as needed
Sertaconazole 2% cream twice daily for up to 4 weeks
Pimecrolimus 1% cream twice daily
Tacrolimus 0.1% ointment twice daily
Betamethasone valerate 0.1% cream or lotion once or twice daily
Desonide 0.05% cream, foam, gel, lotion, or ointment once or twice daily
Fluocinolone 0.01% cream, oil, or solution once or twice daily
Hydrocortisone 1% cream or ointment once or twice daily

Glossary

Calcineurin inhibitor Calcineurin (CaN) is a calcium- and calmodulin-dependent serine/threonine protein phosphatase. Calcineurin inhibitors suppress the immune system by preventing interleukin-2 (IL-2) production in T cells.

Chemotaxis A mechanism by which bacteria efficiently and rapidly respond to changes in the chemical composition of their environment, approaching chemically favorable environments and avoiding unfavorable ones.

Human leukocyte antigen (HLA) The major histocompatibility complex (MHC) in humans, controlled by genes located on chromosome 6. It encodes cell surface molecules specialized to present antigenic peptides to the T-cell receptor (TCR) on T cells.

Psoralen The parent compound in a family of natural products known as furocoumarins. Psoralen is a light-sensitive drug that absorbs ultraviolet (long wave, UVA) light and acts like ultraviolet radiation.

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Acne Vulgaris

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Key Points

- Acne vulgaris is a chronic inflammatory disease that is multifactorial and immune-mediated and affects the pilosebaceous unit consisting of a sebaceous gland and hair follicle [1, 2].
- Acne vulgaris is probably the most common skin disease, affecting 85–100% of the population at some point in life [2].
- Lesions may progress to scarring and despite not presenting any life threat, has sizable psychosocial effects in the setting of low self-esteem and depression among patients [1–3]
- Treatment should be initiated early and with a prolonged course [4, 5].

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Epidemiology

Acne vulgaris is a high-frequency dermatosis affecting more than 40 million people worldwide [1]. It is predominant during adolescence, with an incidence of 79–95%, reaching 100% in both sexes, and is more common in males (70%) than in females (60%). Girls have an earlier onset, with an average age between 11 and 13 years, compared with boys, between 13 and 14 years, with more intense and severe forms [6, 7].

Usually acne vulgaris spontaneously resolves in late adolescence or around 20 years of age. However, currently incidence has increased among adults, mainly females, being 54% in women and 40% in men [6, 8].

It is believed that the degree of acne is directly proportional to the genetic influence, with 88% contribution to the noninflammatory form, and 86–100% for papulopustular and nodule-cystic forms [6, 9]. In patients without skin disease, familial occurrence is 40% [6, 9].

Etiopathogenesis

Acne has a multifactorial etiology that is still not completely understood. It is now believed to be secondary to the interaction of several factors such as follicular hyperkeratinization corroborating the formation of comedones, increased production and quality of sebum, and

colonization of pilosebaceous follicles mainly by *Propionibacterium acnes* and inflammation [3, 4, 10].

Follicular Hyperkeratinization

For a better understanding of the pathogenesis of acne, it is very important to know the pilosebaceous structure [11]. The sebaceous glands are present in all areas of the human body except for the palmoplantar regions [11].

In acne vulgaris, sebaceous follicles are the main affected structure, with primary distribution in the regions of the face, back, and chest [4]. A sebaceous follicle consists of a follicular infundibulum, divided into an acroinfundibulum distally and an infrainfundibulum proximally by the sebaceous gland and sebaceous gland duct that joins the infundibulum [11].

The size and quantity of sebaceous glands are acquired by hereditary means, and their activity increases during adolescence as a result of hormone production [10].

During follicular hyperkeratinization, follicular hyperproliferation of the keratinocytes occurs, with a reduced the scaling rate, increased production of corneocytes, and increased adhesion between them as a result of the increased cohesion of desmosomes [12, 13]. However, the exact mechanism responsible for these changes has not been fully demonstrated [14].

It is believed that hormonal stimuli, proinflammatory cytokines such as interleukin (IL)-1α, follicular deficiency of linoleic acid and integrins [15], and biofilm production by *P. acnes* [16] are responsible for such as changes. Finally, the hyperkeratinization process obstructs the infundibulum with keratin and sebum, in its proximal portion, which leads to the formation of the comedo [10].

Sebaceous Hypersecretion

Sebaceous glands are activated by the action of androgens that originate from the adrenal gland,

ovaries, and testes and are produced by the pilosebaceous unit via dehydroepiandrosterone (DHEA) and androstenedione conversion into testosterone and dihydrotestosterone by the 5α-reductase, 3β-hydroxysteroid dehydrogenase, and 17-hydroxysteroid dehydrogenase enzymes [10, 17].

Sebum hypersecretion can occur as a result of increased sebaceous gland response to hormones through the increase in gonadal and adrenal androgens; or their free portion, as a result of decreased sex hormone binding globulin (SHBG) [4, 10].

Another mechanism responsible for increased sebum production is the stimulation of growth hormones in the liver, which leads to increased production of insulin-like growth factor 1 (IGF-1), responsible for stimulating the production of androgens by the adrenal gland and lipogenesis [18].

In addition to the increased production of sebum there is a change in its composition. It is originally composed of a mixture of lipids such as cholesterol, squalene, fatty acids, steroids, esters, and triglycerides [19]. In the patient with acne there is a decrease in linoleic acid and an increase in squalene, besides the production of palmitic, oleic, sapienic, and lauric acids [19].

Inflammation

There is evidence to show that inflammation is present in all stages of the pathogenesis of acne vulgaris, and the type of inflammatory response corresponds to the clinical state of the patient [20]. The pustule occurs when there is a predominance of neutrophils, whereas in papules, nodules, and cysts there is a prevalence of T-helper lymphocytes, giant cells, and neutrophils [20]. Scars are also an impacted inflammatory response when acne vulgaris is unspecific and early scarring is less evident, but are more intense when specific and with late onset [20].

The changes in sebum composition with decreased linolenic acid causes loss of function of the epidermal barrier and, thus, the release of IL-1α and penetration of proinflammatory fatty

acids and microorganisms in the dermis, besides an increase in lymphocytes and tumor necrosis factor, all of which contribute to the inflammation of acne vulgaris [10].

Colonization of the Pilosebaceous Follicle

There are three major microorganisms found on the skin: *P. acnes*, *Staphylococcus epidermidis*, and *Malassezia* spp. [15]. In acne vulgaris the main bacterium involved is *P. acnes*; to date, there is no evidence of pathogenicity of other microorganisms [10].

P. acnes is a Gram-positive bacillus of facultative anaerobic, diphtheroid type, which is nonspore-forming [16, 21]. It is mainly distributed in areas with higher sebum production, such as the face and upper trunk [3].

The pathogenicity of *P. acnes* is given by the production of proinflammatory mediators, and participation in the formation of comedones and their rupture through lipases [10, 11, 16]. Interaction with the innate immune system still occurs by promotion of an inflammatory response [10, 11, 16].

One of the action mechanisms of *P. acnes* on innate immunity is through toll-like receptors, which are responsible for the recognition of microorganisms by monocytes, macrophages, and polymorphonuclear cells [10, 11]. When activated, they trigger the inflammatory response by producing tumor necrosis factor, interferons, IL-6, -8, -12, and -1β, and chemotactic factors, culminating in the degradation of the bacterial cell array [10].

Antimicrobial peptides (cathelecidins, defensins, and granulysin) are also released secondary to toll-like receptor activation, which functions as epithelium protection, particularly by β-defensin-2, which protects invasion of the pilosebaceous unit by *P. acnes* [10, 11].

Another receptor activated by innate immunity when in contact with *P. acnes* is the nodlike3 receptor that interacts with nuclear factor κB and activates the caspase-1 cascade, releasing proinflammatory cytokines such as IL-1β and IL-18 to intensify the inflammatory process [10].

There is also a humoral immunity response involved in the inflammation of acne vulgaris, namely the production of anti-*P. acnes* antibodies, whose presence is proportional to the severity of the disease [3].

Nowadays it is well known that the main factor responsible for the pathophysiology of acne vulgaris is the presence of *P. acnes* causing activation of the inflammatory response [10].

Other Factors

Diet

The importance of diet in the emergence and worsening of acne is currently much discussed. In the past this association was not considered important. However, the contrast of the presence of acne vulgaris between Western and Eastern societies suggests that diet may be a relevant factor and, consequently, recent studies have shown some associations [2, 22–24].

The increase in the glycemic index in diets causes the increase in basal insulin and IGF-1 values, which contributes to increased production of androgens and leads to overproduction of sebum and follicular hyperkeratinization [24]. The opposite also seems true in patients with hyperinsulinemia, in whom a diet with low glycemic index leads to improvement of lesions [25].

Other foods that seem to be involved in the worsening of acne vulgaris are milk and dairy products because they lead to an increase in IGF-1 besides having precursors of 5α-dihydrotestosterone and growth hormones in their formulas [26].

Regarding essential fatty acids, there is no consensus in the literature; populations with diets rich in fish appear to have less acne compared with the general population, but such data are still under study. It is believed that oral supplementation with essential fatty acids may influence, in a subtle way, the level of fatty acids present in sebum [18, 27, 28].

However, more studies are needed to confirm the true correlation between diet and the presence of acne vulgaris.

Menstrual Period

Two days before the start of the menstrual period, the diameter of the opening of the pilosebaceous follicle decreases, leading to lower flow of sebum to the skin surface and, thus, worsening of acne [2].

Other factors that seem to aggravate the injury are emotional stress, smoking, and use of comedogenic makeup [2, 10], although studies are lacking.

Clinical Presentation and Classification

Acne presents pleomorphic lesions with different clinical conditions from individual to individual, and is divided into noninflammatory and inflammatory lesions [11].

Noninflammatory lesions consist of microcomedones, and closed and open comedones; the microcomedones cannot be viewed and are correlated with severity of the clinical picture. Closed comedones are normochromic to whitened papules about 1 mm in diameter, most commonly viewed by palpation or stretching of the skin [4, 11] (Fig. 21.1). Open comedones are black spots secondary to follicular dilation, being caused by the dark pigment of melanin deposits and lipid oxidation [4, 11].

Inflammatory lesions are made up of papules, pustules, nodules, and cysts [11]. The papules are erythematous lesions of about 5 mm; pustules are similar to papules but with sterile pus at its center [4] (Figs. 21.2 and 21.3). Nodules are erythematous lesions larger than 5 mm that are hardened with dense inflammatory process, which may

Fig. 21.2 Erythematous papules and pustules in the face

Fig. 21.1 Closed comedones in the forehead

Fig. 21.3 Erythematous papules and pustules in the face

indicate greater severity, with deeper cysts consisting of pus and serosanguinous fluid [4, 11] (Fig. 21.4).

Over the years the classification of acne vulgaris has changed and, to date, there is no globally accepted form [4]. The most commonly used classification progresses the forms from levels I to V for noninflammatory and inflammatory acne [4]. The latter is further subdivided into comedonic (noninflammatory), papulopustulous, nodular-cystic, conglobate, and fulminating acne, with gradually worsening severity [4, 6].

Conglobate acne is a severe form with an intense inflammatory process that may lead to drainage of mucopurulent or hematic secretions [4] (Figs. 21.5, 21.6, and 21.7). Fulminating acne occurs predominantly in males, with an abrupt onset and very severe disease, ulcerous-hemorrhagic and necrotic lesions, and is associated with weight loss, fever, prostration, myalgia, and arthralgia, which may impair kidney and liver function as well as bone structure [4, 11].

Fig. 21.5 Papules, pustules, nodules, and cysts in the face and trunk

Fig. 21.6 Papules, pustules, nodules, and cysts in the face and trunk

Fig. 21.4 Erythematous papules, pustules, and nodules in the face

Fig. 21.7 Papules, pustules, nodules, and cysts in the upper trunk

Diagnosis

> Diagnosis of acne is imminently clinical.

Complementary Examinations

It is rarely necessary for histopathology to confirm the diagnosis. Other additional tests may be required depending on specific acne variants.

Differential Diagnosis

Diagnosis is imminently clinical but owing to polymorphism of the lesions, there may be diagnostic quandaries in some patients. The noninflammatory lesions may resemble milia, keratosis pilaris, flat warts, molluscum contagiosum, and syringomas [2]. The papulopustulous forms must be distinguished from folliculitis, medication-mediated acne, perioral dermatitis, and rosacea [2]. The nodular-cystic form may be confused with facial pyoderma, furunculosis (boils) and abscesses, Sweet's syndrome, tumid lupus, Jessner–Kanoff lymphocytic infiltrate, and insect bites [2].

Treatment

Treatment should start as early as possible to minimize scars and psychological complications of the disease, which are closely related to the clinical form presented by the patient [29].

Aims include to correct the follicular hyperkeratinization, decrease sebaceous hypersecretion, and reduce the population of *P. acnes* and the inflammatory process [4].

Topical Treatment

Retinoids

Retinoids act on follicular hyperkeratinization and possess anti-inflammatory effects, reducing the formation of microcomedones and potentiating the penetration of other drugs. By acting in both follicular keratinization and inflammatory process, they are considered the first-line treatment for all forms of acne [3, 4].

They may have some side effects including local irritation, erythema, dryness, and flaking [11]. Available agents include tretinoin, adapalene, tazarotene, and isotretinoin [11]. In general they are not indicated in pregnant women [11].

Among retinoids, adapalene has lighter comedonic properties than tretinoin and therefore is better tolerated by patients [11]. Generally application at night is recommended, starting with low concentrations that are gradually increased [11]. Sometimes its use is recommended on alternate nights for patients with irritative skin conditions [11].

Bactericidal and Bacteriostatic Agents

These agents were introduced to the therapeutic arsenal of acne vulgaris for the control of the *P. acnes* population, and include erythromycin, clindamycin, benzoyl peroxide, and azelaic acid.

Benzoyl peroxide is an antibacterial agent that reduces the population of bacteria by oxidative mechanisms, reduces the formation of comedones, and has an anti-inflammatory action [4, 5]. Its advantage is that it does not induce bacterial resistance and is inexpensive [30]. Adverse effects are similar to those of retinoids and may also lead to whitened clothes and hair [30].

Erythromycin and clindamycin are bacteriostatic agents with anti-inflammatory action and should be used for a 6- to 8-week period, but have discrete adverse effects [4]. Benzoyl peroxide is recommended to be used concomitantly with these agents or alone, in pulses of 5–7 days, to reduce bacterial resistance [29].

Azelaic acid has bactericidal action and thus reduces the inflammatory acne, besides presenting comedolytic and whitening activity, and is safe during pregnancy and breastfeeding [5].

In inflammatory forms a bactericidal/bacteriostatic agent should be added to therapy to increase the effectiveness of the treatment, and antibiotics must be interrupted when inflammatory lesions begin to convalesce [29]. If not possible, replacement of antibiotics by benzoyl peroxide should be considered [29].

According to current knowledge the best form of treatment for acne vulgaris lies in combination therapy, with a combination of a retinoid and a bactericidal/bacteriostatic agent of choice being used for nearly all clinical forms [29]. Such combined treatment achieves faster and more complete results compared with monotherapy [29].

Salicylic Acid

Salicylic acid is used in the treatment of mild inflammatory and comedonic acne. Adverse effects include scaling and erythema [11].

Systemic Treatment

Antibiotics

Antibiotics are commonly given for cases of moderate to severe acne that does not show significant improvement with topical treatment [29, 31], The action mechanism aims to decrease the population of *P. acnes*, thus reducing the formation of inflammatory substances of bacterial origin and decreasing neutrophil chemotaxis, cytokine production, and macrophage activity [4, 11].

The first line of treatment includes tetracycline 500 mg 12/12 h, doxycycline 50–100 mg 12/12 h, lymecycline 150–300 mg 1×/day, minocycline 50–100 mg 1×/day [5]. Second-line treatment includes erythromycin 500 mg 12/12 h, trimethoprim 300 mg 12/12 h, and trimethoprim-sulfamethoxazole 800/160 mg 12/12 h [5].

Currently there is great concern about bacterial resistance, and it is believed that resistance can include nontargeted bacteria [29]. Bacterial resistance appears to be more common in patients with moderate to severe acne [29]. Therefore, the use of antibiotics must be judicious and limited; if the patient does not show good response to treatment, this should be stopped and if there is good response, a maximum of 8–12 weeks of treatment is recommended [29, 32]. In addition, antibiotics should not be used in monotherapy and combination with topical medicine is necessary, except for the topical antibiotics [29, 32].

In general, antibiotics are well tolerated by patients and the most common side effect is gastrointestinal intolerance [4, 5]. Tetracyclines are contraindicated during pregnancy, lactation, and infancy because it interferes in the axial growth of the fetus and changes the color of enamel [5]. Minocycline can cause photosensitivity reactions, skin and mucous hyperpigmentation, and drug-induced lupus [5]. Doxycycline can cause hypersensitivity reactions and lymecycline can cause Stevens–Johnson syndrome [4].

Hormonal

Hormones are considered second-line therapy for female patients with acne, especially adult women [11]. Oral contraceptives as well as spironolactone are intended to block the production of androgens in the adrenal and ovarian glands and thus reduces sebum production [11]. Spironolactone can be used at a dosage of 100–200 mg a day for a period of 2–24 months [5].

Hormonal therapy details are addressed in "Variants of Acne" with regard to acne in the older woman.

Oral Retinoids

Isotretinoin (13-*cis*-retinoic acid) was introduced to acne treatment in 1976 in Europe and in the 1980s in the United States [5]. It is considered quite effective and is indicated for persistent cases of severe acne, nodular acne, and acne conglobata at risk of permanent scarring and resistant to prior therapies [33].

It features actions in all pathologic mechanisms of acne vulgaris, reducing the volume and secretion of the sebaceous glands; normalizing follicular hyperkeratinization, thereby reducing the production of microcomedones; and reducing *P. acnes* growth. It also has anti-inflammatory activity [4, 5, 11].

The recommended dosage varies from 0.5 to 2 mg/kg per day, with a total cumulative dose of 120–150 mg/kg; duration can vary from 6 to 8 months [4, 11]. For cases of severe inflammatory acne it is recommended to lower the initial dose in order to avoid exacerbation of lesions for the first month [4, 5, 11].

The drug is contraindicated in patients with hypervitaminosis A, uncontrolled dyslipidemia,

hepatic failure, and during pregnancy and lactation [33]. It should be used with caution in cases of renal insufficiency or diabetes [33].

Among the adverse effects are dry skin and mucous membranes, facial erythema, eczema, photosensitivity, hair loss, myalgia, arthralgia, photophobia, worse night vision, nausea, colitis, pancreatitis, abnormal liver function, hyperlipidemia, worsening acne condition ("flare-up"), mood swings, and pseudotumor cerebri syndrome when associated with the use of tetracyclines [5, 33]. It is very important that the clinician explains to the female patient the risk of teratogenicity of the drug, excludes the possibility of pregnancy prior to use, follows up with monthly β-HCG tests, and indicates the need for contraceptive use during treatment and 1 month after its completion [33].

After treatment, recurrence can take place in about 20% of cases, particularly in male patients with early onset, severe acne, and family history [34]. New cycles of isotretinoin may be needed, although some patients respond to conventional therapy [34].

For long-term success of treatment, maintenance therapy is indicated, which is beneficial to patients when maintained for a long period, but there is no consensus in the literature regarding the appropriate time frame [29]. The main therapeutic indication is avoidance of topical retinoids and topical antibiotics because of the risk of bacterial resistance [29].

New Therapeutic Strategies

Lasers are currently receiving some attention for their use in inflammatory acne, when used in conjunction with conventional therapy or for those patients not tolerating such therapy [29]. The aim of this therapy is to reduce the population of *P. acnes* and sebaceous gland function [29]. Despite being a promising therapeutic option, more studies on laser therapy are necessary; at present there is insufficient information to recommend such therapy [29].

Complications

The most common complication in patients with acne is scarring, which can result in both mild and severe forms [29]. It is therefore not possible to predict which patients will progress to scarring [29].

Lesions may be epidermal with erythema and changes in skin pigmentation, or dermal with atrophic, hypertrophic, or keloid scars. Multiple treatment techniques are available nowadays, the combination of which may be required for best results. Some examples are dermabrasion, chemical peels, laser therapy, and surgical techniques [29].

Variants of Acne

Fulminant Acne

A severe form of acne, fulminant acne is a rare condition, more common in male adolescents [35, 36]. It occurs in patients with mild or moderate acne who are resistant to conventional therapy [37, 38]. It is an acute condition of systemic involvement and may include fever, myalgia, polyarthralgia, asthenia, hepatosplenomegaly, weight loss, lytic bone changes, neutrophilic leukocytosis, and altered laboratory inflammatory markers [35, 37]. The lesions are inflammatory, painful, and ulcer-hemorrhagic, being more frequently found on the chest and face [35, 39].

It presents unknown etiology, probably influenced by genetic, infectious, and immunologic factors related to the development of reaction type III and/or IV to *P. acnes* [35, 58]. Isotretinoin is a possible disease precipitant, since it leads to the fragile epithelium of the pilosebaceous duct and allows contact of *P. acnes* with the immune system [40].

It has no response to conventional acne treatment, and the use of oral antibiotics is ineffective in the absence of secondary infection [35]. Hospitalization may be required [40]. The treatment is typically oral prednisolone, 0.5–1 mg/kg/

day for 4–6 weeks, isotretinoin being introduced from the fourth week of corticosteroid therapy [35, 37]. Other options are dapsone, 50 mg/day, or infliximab [40].

Acne in Adult Women

Acne in adult women (AAW) is defined as the presence of acne in women older than 25 years [41]. Its prevalence is steadily increasing, although it is unclear whether this increase is a true one or whether it is due to greater access to information about the disease and treatment, which leads to increased demand for specialized care [42].

Classification and Clinical Presentation

Patients with AAW can be divided into two groups [8]:

- Persistent acne: most common clinical form, beginning in early adolescence and continuing into adulthood [8].
- Late-onset acne: Begins after 25 years of age and involves two subgroups: acne on the chin, with lesions mainly around the perioral region with emergence and worsening during premenstrual period, and sporadic acne, of sudden onset and usually without any apparent cause [8].

The clinical presentation shows a predominance of inflammatory lesions with the presence of papules and pustules, in most cases showing a light to moderate presentation of the disease and refractory to treatment [41, 43] (Figs. 21.8 and 21.9). Lesions are located generally in the lower third of the face and "U" zone of the neck [41].

Fig. 21.8 Erythematous papules on the face

Fig. 21.9 Erythematous papules on the face

Affected women show sensitive skin with postin-flammatory erythema and hypo- or hyperpig-mented scars [43, 44]. The involvement and cosmetic changes on the face have made AAW a disease of great psychological and social impact, strongly compromising patients' quality of life [8, 41].

Pathophysiology

AAW is a multifactorial and incompletely under-stood disease, influenced by several external fac-tors: smoking; obesity; emotional stress; endocrinologic abnormalities such as polycystic ovary syndrome (PCOS) and insulin resistance; drugs (benzodiazepines, lithium, cyclosporine, corticosteroids, progestins and oral contracep-tives, isoniazid, ramipril, and vitamin B com-plex); food with high glycemic load and dietary supplements rich in amino acids; exposure to UV radiation; and use of occlusive cosmetics [41, 43, 45].

To understand the pathophysiology of AAW, one should take into account that the production androgen derived from cholesterol occurs in gonads, adrenal glands, and peripheral tissues, including the skin, which is the area of greater production of androgenic substances [44, 46]. DHEA sulfate (DHEA-S) produced in the adrenal gland is converted to testosterone, which in turn is converted to dihydrotestosterone (DHT) [46]. DHT is a more potent androgen whose production occurs in the sebaceous glands in the presence of the 5α-reductase 1 enzyme [46].

When there is an association with hyperan-drogenism, the most frequent causes are PCOS and adrenal hyperplasia of delayed onset and, in addition to acne, there may be the presence of hirsutism, alopecia, changes in voice, menstrual irregularities, and infertility [42, 47]. Facing sus-picion, there should a serum dosage during the follicular phase of the menstrual cycle of free and total testosterone, DHEA-S, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) in addition to transvaginal ovary ultrasonography [47, 48].

However, the changes seen in patients with AAW resulting from hyperandrogenism occur without the presence of associated endocrine disease, laboratory abnormalities, or menstrual irregularity [42].

The principal factor involved in AAW is increased activity of the sebaceous glands whereby circulating androgens at normal levels act in an exaggerated form in the sebaceous glands by increasing 5α-reductase enzyme activ-ity, associated with hypersensitive hormone receptors in sebocytes and keratinocytes [8].

Peripheral hormonal conversion is also increased, producing the most potent andro-genic hormones such as testosterone and DHT [43, 48].

In addition, peripheral insulin resistance and hyperinsulinemia cause increased IGF-1, which stimulates the production of ovarian androgens and influences the availability of active circulat-ing hormones, therefore reducing the hepatic pro-duction of SHBG and, thus, providing a greater amount of free androgens [49].

Finally, there is an association with a genetic factor attributed to the presence of familial cases in more than 50% of AAW cases [50]. Genetically determined changes occur in molecules involved in innate immunity by inducing reduction of *P. acnes* resistance and chronic inflammation of sebaceous glands [43, 50, 51].

Treatment

AAW follows the general lines of treatment of acne vulgaris [41].

For mild cases, topical agents are used long term, prioritizing simple-to-use agents with good tolerance to obtain adherence of the patient [41, 52].

Topical Treatment

- Topical retinoids: keratolytic action is the best option for maintenance, and adapalene is mostly used and well tolerated [8, 52].
- Benzoyl peroxide: bactericidal, anti-inflammatory, and keratolytic action, often used in combination with other topi-cals [53].
- Azelaic acid: hyperkeratinization normalizes and reduces the proliferation of *P. acnes*, reducing inflammation. Not considered first-line treatment [54].

Systemic Treatment

For more inflammatory, extensive forms and resistance to topical agents, systemic treatment is advised [52].

- Oral antibiotics: preference for cyclin derivatives (tetracyclines, doxycycline, lymecycline), trimethoprim, and macrolides; however, they should not be used for prolonged periods or combined with the use of topical antibiotics, to prevent the induction of bacterial resistance [41, 52].
- Isotretinoin: suitable for severe and resistant forms, can be used in low daily doses to avoid skin irritation in sensitive women [55]. Fails and relapses in 30% of cases [55].

Hormonal Treatment

As an additional option to clinical forms that are unresponsive topical treatment and/or antibiotics, hormonal treatment through the use of oral contraceptives is a viable option, as AAW is an androgen-dependent disease [56]. It is an effective therapy that reduces greasiness of the skin and the number of lesions [57].

- Spironolactone: antiandrogen aldosterone antagonist that has an inhibitory effect on the 5α-reductase 1 enzyme [44, 58]. It can be used individually or in combination with the oral contraceptive form, with optimal clinical response [8, 58].
- Estrogen (ethinylestradiol): directly inhibits sebum production, blocks the hypothalamic-pituitary axis by negative feedback which prevents the production of androgens by the ovaries, and enhances the hepatic synthesis of SHBG, which reduces the free form of active androgens [48, 59].
- Progestins (cyproterone, drospirenone): selective for progestagenic receptors and have antiandrogenic and antimineralocorticoid activity [57]. Ideally used with ethinylestradiol or as an oral contraceptive combined with spironolactone [8].

Side effects of antiandrogens are weight gain, headache, stomach disorders, depression, decreased libido, edema, irritability, melasma, uterine bleeding, and liver abnormalities [60]. Contraindications to its use are the presence of cardiovascular disease, thromboembolic events, pregnancy, genital bleeding, and liver disorders [60].

- Flutamide, an antiandrogen used in the treatment of prostate cancer, and finasteride, an inhibitor of 5α-reductase inhibitors, are not used in the treatment of AAW [57].

For cases with the presence of insulin resistance metformin can be prescribed to sensitize tissues to insulin action, thereby controlling the action of IGF-1 [61].

Pediatric Acne

Neonatal Acne

Acne which may occur at birth or within the first 4 weeks of life is known as neonatal acne [62, 63]. It usually affects boys, and there is a predominance of closed comedones on the forehead, nose, and cheeks, and, less commonly, inflammatory lesions [64] (Fig. 21.10).

Its etiology is linked to increased sebum excretion, because the sebaceous glands are increased in size at birth because of the increased production of DHEA by adrenal glands during this period, in addition to having the extra stimu-

Fig. 21.10 Closed comedones on the cheeks of an infant

lation of these glands by maternal androgens at this stage of life [62–64]. In boys, testicular androgens provide additional stimulus to the sebaceous gland, which explains the higher incidence in males [62, 65]. Another factor contributing to the framework is the colonization of the sebaceous glands by *Malassezia* spp., causing a local inflammatory response [66].

The differential diagnosis of neonatal acne should include virilization disease, congenital infections, maternal use of medications during pregnancy, such as lithium and hydantoin, and use of topical oils and ointments [67].

Most often no treatment is necessary, since it is a mild and limited condition, with spontaneous resolution in 1–3 months [64]. When necessary, topical tretinoin and azelaic acid can be used for mild cases, and a solution of erythromycin and benzoyl peroxide gel for inflammatory forms [63, 66, 68].

Acne in Infants

Acne in infants affects predominantly male children, and may start at 3–6 months of age or later [64]. Its presence increases the risk of developing acne vulgaris, particularly severe forms, in adolescence [6]. It affects the face, most often on the cheeks, presents more pleomorphic and inflammatory lesions than neonatal acne, and also can present papules, pustules, nodules, and cysts [67].

Its causes are due to hyperandrogenism by increased production of androgens in the fetal adrenal glands and testicles, in addition to having the child's skin colonized by *Malassezia* spp. [62].

The differential diagnosis of infantile acne should include diseases that cause virilization, chloracne, and acne induced by the use of creams, lotions, and oils [67].

Most cases resolve spontaneously or with treatment while others remain active until adolescence [62, 67]. The treatment follows the same guidelines of acne vulgaris, using retinoids or topical benzoyl peroxide [66, 68, 69]. When use of oral antibiotics is necessary, erythromycin is the first choice [67]. Tetracyclines are contraindicated until 8 years of age in view of the risk of causing dental changes [66].

Occupational Acne

Elaioconiosis

Elaioconiosis is an acneiform eruption caused by occupational exposure to cutting oils (metal workers) and greases (mechanical) that lead to obstruction of the follicular ostia [70]. Clinically, lesions in the upper limbs are observed, with the presence of comedonic forms with black points in follicular ostia, along with papules and pustules that may be associated with itching and pain [71].

Treatment is slow and the patient should take time off work [71]. The use of a loofah while showering and keratolytics are recommended [71]. Topical or systemic retinoids can be used [71]. The clinical presentation should be prevented with the use of silicone creams, frequent handwashing, appropriate working clothes, and use of personal protective equipment [72].

Chloracne

Chloracne is a severe form of occupational acne caused by environmental contamination or industrial use of chlorinated hydrocarbons included in pesticides and oil products [70, 73]. It begins with redness and swelling on the face, posteriorly presenting noninflammatory comedones, cysts, and scarring on the face and neck [74, 75]. As this disease is caused by intoxication, systemic manifestations can occur, such as fatigue, anorexia, arthritis, neuropathy, and liver disease, among others [75, 76].

After exposure, symptoms begin in 2–4 weeks, but full recovery takes around 2–3 years, as the causative agents are lipophilic and have slow body clearance [74]. Chloracne is resistant to treatments commonly used in acne vulgaris [74]. Exposure to toxic agents should be prevented and if it occurs, the worker should be removed from the site and elimination of the substance should be attempted [74]. The use of Olestra (synthetic substitute of dietary fat) accelerates the fecal elimination of hydrocarbons by up to 30-fold [77].

Acneiform Eruptions

Follicular lesions similar to acne caused by substances in contact with skin or systemic agents

are known as acneiform eruptions [78], which present an inflammatory initial lesion with the emergence of erythematous papules, but can still present pustules and nodules mostly on the face, trunk, proximal limbs, and buttocks [79].

Unlike acne there is no follicular hyperkeratinization, but inflammatory pilosebaceous follicles are noticed [78]. It is of sudden onset and can occur at any age; lesions have a monomorphic aspect and are disseminated, with acute or subacute evolution; Besides the absence of comedones, lesions may be accompanied by systemic signs of toxicity which improves after removal of the cause [45, 79, 80].

Agents responsible for the disease: systemic and topical medications; cosmetics made with fatty vehicles (leading cause in women); halogenated chemicals (chloracne); excessive hygiene with products based on fatty acids or hexachlorophene; friction caused by exfoliating cosmetics, banners, hats, and caps; heat, excessive sun exposure, and use of greasy sunscreens; occupational agents such as oils or greases (elaioconiosis) [81, 82].

The differential diagnosis of acneiform rash should include acne vulgaris, rosacea, and folliculitis [79, 80]. For successful treatment it is necessary to remove the causative agent and use topics such as benzoyl peroxide and retinoids combined or not with antibiotics; the use of systemic medications such as isotretinoin and antibiotics at low doses may be required [45, 82].

Drug-Induced Acne

Acneiform eruption most often occurs as an iatrogenic side effect of systemic or topical medications [78]. Some drugs are excreted by the sebaceous glands with follicular high concentration, and can be cytotoxic and cause an inflammatory reaction [79].

Causative agents are: corticosteroids; B vitamins; hormones (contraceptives, androgens, gestrinone, corticotropin, and thyroid drugs); antiarrhythmics; anticonvulsants (hydantoin); drugs with lithium base; halogens (iodine, bromine, fluorine, and chlorine); phenothiazines and diazepam; quinine; tuberculosis drugs (isoniazid, rifampicin, ethionamide); antibiotics (tetracycline and streptomycin); cyclosporin; azathioprine; biological chemotherapeutics of the type antireceptor monoclonal antibodies of the epidermal growth factor receptor used in the treatment of various cancers (cetuximab, erlotinib, gefitinib); sirolimus (immunosuppressant used in transplants) [78, 80, 81].

Along with erythematous papules of follicular location, punctate vesicles in the center of the papules may be present [81]. Itching is a common symptom [82]. The treatment is the same as for any other acneiform rash and is based on the removal of the causative agent [80]. Antihistamines can be used in cases with accompanying pruritus [81].

Glossary

Comedo A hair follicle infundibulum that is dilated and plugged by keratin and lipids. The lesion is referred to as an open comedo when the pilosebaceous unit is open to the surface of the skin with a visible keratinaceous plug. A closed comedo occurs when the follicular opening is unapparent and accumulates whitish keratin.

Cyst An encapsulated cavity or sac lined with a true epithelium that contains fluid or semisolid material (cells and cell products such as keratin).

Nodule A solid round or ellipsoidal, palpable lesion of diameter larger than 0.5 cm. Depth of involvement and/or substantive palpability, rather than diameter, differentiates a nodule from a large papule or plaque. Nodules are of five main types: epidermal, epidermal-dermal, dermal, dermal-subdermal, and subcutaneous.

Papule A solid, elevated lesion less than 0.5 cm in size in which a significant portion projects above the plane of the surrounding skin.

Pustule A circumscribed, raised cavity in the epidermis or infundibulum containing pus; may contain bacteria or be sterile. Pustules may vary in size and, in certain situations, may coalesce to form lakes of pus.

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Rosacea

22

Renan Rangel Bonamigo, Wagner Bertolini, and Sérgio Ivan Torres Dornelles

Key Points Summary
- Rosacea is a frequent chronic dermatosis and may heavily affect the quality of life
- Dermatosis is prevalent on the face and often starts mainly in the intermediate age range
- Rosacea pathogenesis is complex: neurovascular, inflammatory, and dermal deconstruction, with many immunologic mediators
- Clinical subtypes of rosacea are erythematous telangiectatic, papulopustular, phymatous, granulomatous, and ocular.

- Treatment aims at control of symptoms, with a focus on nonexposure to triggering factors, and the use of topical and systemic drugs as well as different laser types

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Epidemiology

Despite the large amount of published material, few epidemiologic studies of rosacea have been carried out to date. Most of these studies use different methodologies, populations, and disease definitions. Therefore there is, for example, variation with regard to the prevalence of the disease (between 0.09% and 22%), although the general prevalence is estimated at 10% [1–12]. Most of these studies did not classify rosacea according to its subtypes; the few that did showed a prevalence estimate of around 72–82% for subtype 1 (erythematous telangiectatic rosacea), 18–28% for subtype 2 (papulopustular rosacea), and approximately 1% for subtype 3 (phymatous rosacea), affecting men more than women [6, 10, 13]. Subtype 4, ocular rosacea, can be seen in up to 30% of patients with the other subtypes [14]. An English research study estimated a rosacea incidence of 1.65 per 1,000 persons per year [15].

With regard to distribution by gender, most of the studies indicate equity or a slight female

prevalence [3, 4, 6, 10, 13, 15]. The disease affects mainly Caucasians [16, 17] and adults older than 30 years; it is rare in adolescents and children [5, 15, 18, 19].

Significant predisposition factors for rosacea are ultraviolet (UV) radiation exposure and a large amount of *Demodex folliculorum*, a commensal mite of the pilosebaceous follicle. Other investigated factors include the *Helicobacter pylori* and *Staphylococcus epidermidis* bacteria, although research studies have delivered opposing results [1, 20–23].

A positive family history seems to be a significant risk factor for rosacea [1]. A cohort study with twin brothers was recently published, showing a 50% influence of genetic factors and a 50% influence of environmental factors on rosacea. The study showed a powerful correlation between the scoring levels of the National Rosacea Society (NRS) and age, exposition to UV radiation and fair skin (Fitzpatrick I, II, and III classification); it also showed positive associations between rosacea and body mass index, skin cancer, and cardiovascular disease [24].

Some research studies showed a connection between rosacea and other diseases, such as migraine, depression, and autoimmune diseases [6, 25, 26]. Ingestion of hot beverages or alcoholic drinks, physical exercise, and heat exposure seem to exacerbate rosacea via skin blood vessels [1, 15, 17, 26–28]. An English research study showed a greater risk for rosacea development in nonsmoking persons than in smokers, and a slightly higher risk in former smokers [15].

Most of epidemiologic studies of rosacea conducted to date used adult populations only (working population), predominantly of Caucasian origin; no population-based studies are available using heterogeneous populations.

Etiopathogenesis

Rosacea is a chronic skin disease that affects almost exclusively the central facial region [29, 30]. The exact etiopathogenesis of rosacea remains unknown, although much progress can be acknowledged alongside the appearance of many theories. The main ones are described herein.

Transcriptome Analysis

Epidemiologic data comparing disease and skin phenotype prevalences in different regions suggest that rosacea has a genetic component [1, 31]. A recent analysis of the transcriptome profile of rosacea patients verified the existence of different gene profiles for each disease subtype, although some genes overlap [31–33].

Deregulation of the Innate Immune System

Under normal physiologic conditions the activation of the innate immune system leads to a controlled increase of skin antimicrobial cytokines and peptides. This form of regulation seems to be impaired in rosacea patients [34].

Cathelicidin is the main adenosine monophosphate involved in rosacea; on the skin surface it is subjected to cleavage by the kallikrein-5 serum protease (KLK5) in the LL-37 active peptide (Yamasaki and colleagues 2007). Besides the increased cathelicidin and KLK5 expression, the LL-37 is processed into smaller fragments in rosacea patients [35]. The LL-37 and those fragments function to activate and control immune reactions by increasing the release of cytokines and chemokines by local cells, leukocytes, mastocytes, and keratinocytes [36]; they regulate the expression of the extracellular matrix components and increase endothelial cell proliferation, which may induce a functionally important angiogenesis [37]. Injection of such peptide fragments into the skin of mice led to a "rosacea type" dermatitis, thus lending more support to the theory favoring the pathogenic role of cathelicidins on rosacea [35].

Up to now the least understood part of the pathogenesis is how and which mechanisms lead to the increased cathelicidin and KLK5 in rosacea patients. One of the main responsible elements

would be the high level of the toll-like 2 receptor (TLR2) on the skin, a molecular sensor that triggers immune reactions when activated, such as increased expression level and KLK5 activity level, thus increasing LL-37 and fragment expression [35, 38].

The main TLR2 activators may be *D. folliculorum*-released chitin, a saprophytic mite found in the skin pilous follicle (denser in rosacea patients), and *Bacillus oleronius* Li, a Gram-negative bacterium found in *D. folliculorum* [40, 41].

The metalloproteinases (MMPs) are the other group of molecules that activate KLK5. KLK5 would be released as a pre-proenzime which becomes active after undergoing cleavage by MMP-9. The expression of many MMPs, including MMP-2 and MMP-9, is increased on the skin of rosacea patients [42]. Bonamigo and colleagues found a linear correlation between the presence of *D. folliculorum* and the degree of positivity for MMP-9 expression in rosacea patients' fibroblasts, something not found for MMP-2, and they concluded that MMP-9 may be an explanatory link between the presence of *D. folliculorum* and the clinical expression of some rosacea cases [43].

Muto and colleagues suggested a role of mastocytes in the rosacea inflammatory process induced by cathelicidins [44]. The mastocytes possibly secrete LL-37 and MMP-9 and activate the release of inflammatory cytokines [45].

The LL-37 cathelicidin expression in human keratinocytes is heavily induced by activation of vitamin D. UV light exposure triggers activation of vitamin D in the keratinocytes and the subsequent expression of cathelicidin, which has been mooted to account for the preferred facial topography of rosacea [46]. In a recent research study, Ekiz and colleagues found relatively increased levels of vitamin D in rosacea patients compared with the control group, but larger epidemiologic studies are necessary to verify this finding [47].

Microorganisms

Microorganisms seem to play a significant role, albeit not well understood, in the etiopathogenesis of rosacea. *D. folliculorum*, a mite belonging to the skin microbiota, has been the most widely investigated microorganism [48]. The significance of this parasite is still controversial because they are often found in people without clinical manifestations, and their prevalence may reach 100% in the elderly [49]. However, some research studies identified a prevalence increase in rosacea patients [50]. A meta-analysis showed that mite density and rosacea had a statistically significant association [39].

Nowadays the most relevant hypothesis suggests that the innate immune system favors mite hyperproliferation. The causal relationship of *Demodex* mites with skin lesions as being triggered through many mechanisms is suspected: mites mechanically block follicles, thus leading to their distension or rupture and the triggering of local inflammation [48, 51]; the presence of the chitinous exoskeleton this would act as a foreign body, thus playing a role in granulome formation. Mite-produced residue and/or bacterium-associated residue may activate elements of the innate immune system or stimulate the system through a delayed hypersensitivity reaction mechanism [52]. One of the most acceptable hypotheses is that mite chitin activates TLR2 keratinocytes and then activates KLK5 [34, 53].

Another hypothesis regarding *Demodex* mites in rosacea induction supposes that mites are vectors for other microorganisms that cause and exacerbate skin lesions [54]. Such bacterial endosymbioses could play a significant role in rosacea pathogenesis, which would explain the antibiotic effect on the patients [51]. Lacey and colleagues isolated the *B. oleronius* from *D. folliculorum* and determined the reaction of antigens to rosacea patients' serum but not to those in the control group (healthy subjects). They also identified thermal shock proteins and a lipoprotein in *B. oleronius* antigenic molecules known as TLR2-stimulating agents. According to the hypothesis, mites piling up in the follicles cause follicle distension and damage, thus leading to diffusion of bacterial agents through the follicle walls, resulting in an immunologic reaction [41]. Healthy patients who had their neutrophils exposed to *B. oleronius* showed an increase in the production of

MMP-9, cathelicidin, tumor necrosis factor, and interleukin-8, most of them rosacea inflammatory mediators [55]. Murillo and colleagues, on the other hand, analyzed *Demodex* microbiota through a real-time polymerase chain reaction system and did not identify *B. oleronius*, only a few *Bacillus* spp. [56].

In Australia, Whitfield and colleagues isolated pure colonies of *S. epidermidis* in pustules of 9 out of 15 patients with papulopustular rosacea, whereas they were not isolated in the same patients' adjacent skin with no lesion. Bertolini and colleagues, however, conducted a similar research study in Brazil with 22 patients when such bacteria were not found [20].

Another investigated microorganism in rosacea is the gastric bacterium *H. pylori*, although most of the studies showed contradictory results [57]. A research study by Bonamigo and colleagues concluded that *H. pylori* is a possible risk factor for rosacea in certain groups of individuals, but the previous use of antibiotics to treat rosacea must be regarded as a risk factor for interference in studies on that association, since these drugs are also useful for treating *H. pylori* infection.

Ultraviolet Radiation

The presence of actinic elastosis in rosacea suggests a role of UV radiation in the disease pathogenesis [58]. Despite being postulated as a possible photoinduced dermatosis [59], a recent study that examined exposure time to UV and rosacea prevalence failed in verifying the correlation [5].

UVA light in particular causes MMP overexpression and collagen denaturation, both of which are direct or indirect participants in clinical manifestations of rosacea. UVB light increases the production and secretion of fibroblast growth factor 2 and vascular endothelial growth factor 2 (VEGF2), both playing a role in the skin hypervascularity of rosacea [34].

In addition, significantly high levels of reactive oxygen species (ROS) produced mainly in the skin after UV radiation were noticed in skin samples of rosacea patients [60]. The ROS may account for the initiation of many proinflammatory effects including the expression of cysteine-cysteine 2 (CCL2) and cysteine-X-cysteine 8 (CXCL8) chemokines, thus attracting leukocytes [61], and the activation of the TLR2 receptors, therefore making it easier for the KLK5-cathelicidin inflammatory cascade to spread out [62].

Although acute UV exposure is an indisputable triggering factor for rosacea, it remains unclear as to how much the chronic photodamage plays a part in the disease physiopathology, mainly because photodamage is not a characteristic sign in patients with early rosacea. The dermal architectonic deconstruction possibly plays the main role in chronic UV exposure for rosacea development [45, 63, 64].

Neuroimmune Interactions

The finding of a new class of nonselective cation channels, the transitory receptors of potential channels (TRPs), increased the understanding of how sensorial nerve endings are activated to release vasoactive neuropeptides for pain or inflammation control, with significant implications for rosacea physiopathology. These receptors are clearly expressed in neuronal and non-neuronal tissue including keratinocytes and endothelial cells [65]. Most research studies focus on the vanilloid receptor TRP1 (TRPV1), also known as capsaicin receptor, and on the TRP ankyrin 1 receptor (TRPA1), both involved in pain and inflammation induction [66]. They can be activated by heat, ethanol, spicy food (TRPV1), cold, formalin, and other chemical products (TRPA1), all triggering factors for rosacea. TRPV1 and TRPA1 activation triggers the release of substance P and calcitonin gene-related peptide, important mediators of inflammation and neurogenic pain. Worth noting is the fact that rosacea skin seems to show a significantly lower endurance threshold for temperature and chemical substances by becoming more sensitive than usual [67]. Other less investigated neuropeptides in rosacea are vasoactive intestinal peptide,

somatostatin, neurokinin A, and corticotropin-releasing hormone.

Rosacea sufferers may have a genetic predisposition or some functional gain from a mutating receptor involved in the neurovascular regulation sensitive to the rosacea triggering factors (or TRP overexpression or overstimulation), which results in neuropeptide release (characterized by flushing and edema), followed by erythema (transitory and even persistent) and the recruitment of inflammatory cells to the inflammatory site. The fact that rosacea clinically appears with transitory flushing indicates the involvement or even the main role of the neurovascular system in the early phase of disease [68].

Barrier Abnormal Function

Changes in the physiologic conditions of skin may affect the skin microbiota and its phenotype. It was recently established that the skin of patients with papulopustular rosacea is more acidic and dryer, with a normal fat level, but with a different composition of fatty acids [69]. Ni Raghallaigh and colleagues suggest that the nature of fat, more than its amount, may favor *D. folliculorum* mite development [69].

Epidermal proteases and their inhibitors play central roles in normal skin homeostasis. Matriptase and caspase-14 are essential enzymes for the filaggrin process that has barrier functions in the untouched skin, and the KLK5 and the KLK7 proteases support scaling physiologic processes. In rosacea the increased levels of KLK5 result from TLR2 increase and activation. The increased mediated KLK change of the cathelicidin peptides may lead to an increase of peptides and their fragment levels, which may induce vasodilation and promote leukocyte chemotaxis. Besides, a rise in the amount of serum proteases may result in activation of the TRP supraregulation via and/or activation of the activated protease receptors. In addition, a rise in serum protease activity in rosacea can also be effected by its impaired inhibition. Proteases can control the immune function and induce vasodilation, inflammation, pain, or pruritus [68].

Neurovascular Changes

Activation of the precapillary arterioles in rosacea is followed by vasodilation (flushing, erythema), whereas postcapillary venule activation is followed by protein flight (edema), and leukocyte recruitment via supraregulation of selectins and cell-adhesion molecules. Conversely, after stimulation by VEGF or external stimuli (e.g., UV), the number of blood vessels may increase (angiogenesis) [45, 70].

Activation of α2-adrenergic receptors of the smooth muscle cells of arteries and arterioles (through brimonidine or oxymetazoline, for example) supposedly alleviates rosacea flushing via vasoconstriction and possible anti-inflammatory effects [71, 72].

Expansion of lymphatic vessels, but not lymphangiogenesis, was noticed in all three rosacea subtypes [45]. The early involvement of lymphatic vascular dilation is intriguing even in subtypes with clinically unrecognizable edema, and not only in clinically relevant lymphedema. To date no theory on the physiopathogenesis seems capable of explaining these lymphatic vessel changes in rosacea [68].

Neuromediators

The analysis of the classic neuromediator and receptor genes showed that many neuropeptides, vasoactive amines, or TRPs involved in vasoregulation and pain may also be expressed by skin-dwelling cells and/or by immunologic system cells. PACAP (pituitary adenylate cyclase activating polypeptide), one of the most powerful vasodilators in humans, is increased in all rosacea subtypes up to more than 20-fold, and is capable of being released by activated endothelial cells and degranulated mastocytes [73]. Other supragranulated neuroreceptors are the HTR3A serotonin receptor, the H2R or H3R histamine receptors, and the adrenomedullin receptor. Differently from these, NK1 is not supraregulated, and the expression levels of the TRPV ionic channels show large variation. Serotonin (5-hidroxytriptamine), the important inflammatory and neurosensory mediator, is released by mastocytes, platelets, and other cells,

and its role has been under investigation in many inflammatory skin diseases [45, 74]. The precise role of these mediators and receptors on the physiopathology of all rosacea subtypes, including ocular rosacea, still needs to be clarified.

Clinical Presentation

Rosacea is mainly a facial dermatosis, with other topographies seldom affected (cervical and thoracic regions, scalp, and upper limbs).

Theoretically there must be a permanent facial erythema and history of sudden and repeated episodes of vasodilation (known as flushing) [75]. Injuries belonging to the classic presentation include telangiectasias, inflammatory lesions (papules, nodules with or without pustules), and injuries resulting from dermal hyperplasia and sebaceous hypertrophy (phymas). Ocular changes may also be part of rosacea presentation, therefore providing disease verification.

According to the NRS, the presence of one or more than one primary characteristics, with distribution over the central region of the face, would prompt a rosacea diagnosis. Frequently, the secondary characteristics appear with one or more than one primary characteristics, although they may occur on their own. Box 22.1 summarizes the clinical manifestations according to the NRS.

Four subtypes and one variant of rosacea were described based on the presence of these primary and secondary characteristics. Although it has long been known that the patient may display multiple subtypes simultaneously, the progression from one subtype to another is still controversial [76].

- *Subtype 1 – Erythematous telangiectatic rosacea* (*ETR*): characterized by persistent and facially centered flushing and erythema. The telangiectasias are common but not central to the diagnosis. Edema of the central region of the face and report of burning, pricking, skin roughness, and scaling may occur. History of isolated flushing is common in patients [32] (Fig. 22.1).
- *Subtype 2 – Papulopustular rosacea* (*PPR*): includes persistent erythema with papules, pustules, or both, allotted over the central region of the face, possibly occurring periorificially (perioral, perinasal, periocular). It recalls acne vulgaris except for the absence of comedones. Pricking and burning sensations may occur. This subtype is often connected to subtype 1 [32] (Fig. 22.2).
- *Subtype 3 – Phymatous rosacea* (*PR*): thickened, fibrous skin with nodules, and irregular and increased skin surface. The nasal region is mainly affected, although the mentum, the forehead, the malar, and the auricle regions may be affected (Fig. 22.3). This subtype may occur as a combination of the two previous subtypes [32].

Box 22.1 Clinical criteria and rosacea diagnosis

Primary characteristics:

≥1 with central facial distribution:

  Flushing (transitory erythema)
  Non-transitory erythema
  Papules and pustules
  Telangiectasias

Secondary characteristics:

  Burning or pricking sensations
  Platelet injuries
  Seeming skin dryness
  Edema
  Ocular manifestations
  Peripheral location
  Phymas

Fig. 22.1 Rosacea, subtype 1: erythematous telangiectatic rosacea

Fig. 22.2 Rosacea, subtype 2: papulopustular rosacea

- *Subtype 4 – Ocular rosacea* (*OR*): the diagnosis has to be considered when one or more than one of the following signs or symptoms are detected: interpalpebral conjunctival hyperemia, foreign body sensation, burning and pricking sensations, dryness, pruritus, light sensitivity, blurred vision, conjunctival and eyelid margin telangiectasia. Blepharitis, conjunctivitis, and irregular eyelid margins may also occur. Chronic staphylococcal infection (hordeolum) and chalazion possibly resulting from a dysfunctional Meibomian gland are signs of ophthalmopathies associated with rosacea. Skin symptoms are usually present although they are not crucial requirements for ocular rosacea diagnosis, considering that in about 20% of patients eye signs are displayed earlier than skin signs [32].

Fig. 22.3 Rosacea, subtype 3: phymatous rosacea

- *Variants*: *granulomatous rosacea* (*GR*), characterized by monomorphic, hard, orange, brown, or erythematous papules or nodules, mainly located on the malar regions and periorificial areas, possibly leading to scars. The lesions are less inflammatory than the subtype 2 lesions, often located on a normal skin base. There is no need of other rosacea signs to diagnose this variant. Owing to physiologic differences the following conditions were excluded as rosacea variants: fulminans rosacea (facial pyoderma), and acneiform eruption induced by steroid and perioral dermatitis [32] (Fig. 22.4).

To improve the patient's assessment the clinical presentation of rosacea can be classified as mild, moderate, or severe, although those definitions lack more objectivity.

Complementary Examinations

In the eventuality of clinical characteristics not granting a diagnostic definition, histologically detected dermal changes may be useful [77].

Histologic findings of rosacea include: dilation of blood and lymphatic vessels leading to erythema and edema; perivascular infiltrate resulting from increased T cells, macrophages; and frequently (but not exclusively) actinic elastosis, edema, and crooked and dilated vessels.

Fig. 22.4 Rosacea, granulomatous variant
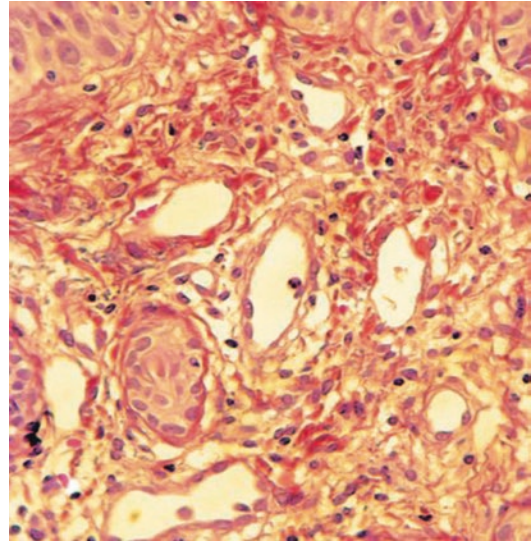
Fig. 22.5 Rosacea histopathology: dermal inflammatory infiltrate and "microaneurysms" (hematoxylin–eosin, ×400) [77]

Box 22.2 Rosacea diagnosis

1 or more: flush (transitory erythema); nontransitory erythema; papules and pustules; telangiectasias

Subtypes and variant

Secondary characteristics may help

Histopathology may help

The papulopustular form may also show a dense perifollicular infiltrate composed of neutrophils and macrophages [74, 78]. The phymatous form shows sebaceous gland hyperplasia, follicular plugs, telangiectasias, and noticeable dermal thickening and fibrosis, besides large mucin stores [79].

Bonamigo and colleagues [77] noted the main histopathologic characteristics of rosacea: dermal, vascular neoform, and vascular dilations resulting in true "microaneurysms" (Fig. 22.5). Moreover, frequent findings encompass deconstructed dermal framework and elastosis. The presence of the *D. folliculorum* mite (Fig. 22.6), with circumjacent inflammatory process was noted in 12 rosacea patients (35.3% of the sample) and two control patients (6.9%). The difference found between cases and controls regarding the presence of *D. folliculorum* was statistically significant ($p < 0.05$).

Diagnosis

Rosacea diagnosis is basically clinical (Box 22.2)

Differential Diagnoses

Because of its varied clinical forms, rosacea has many differential diagnoses; we list the main diagnoses according to subtype in (Box 22.3). It is worth noting that some diseases may act as a differential diagnosis for more than one subtype and that it is not rare for a patient to show those diseases concomitantly with rosacea.

Box 22.3 Rosacea differential diagnoses

ETR	Seborrheic dermatitis
	Lupus
	Chronic use of steroids
	Contact dermatitis
	Atopic dermatitis
	Dermatomyositis

Fig. 22.6 Rosacea: *Demodex folliculorum* (hematoxylin–eosin, ×250 a zoomed-in detail, ×40) [77]
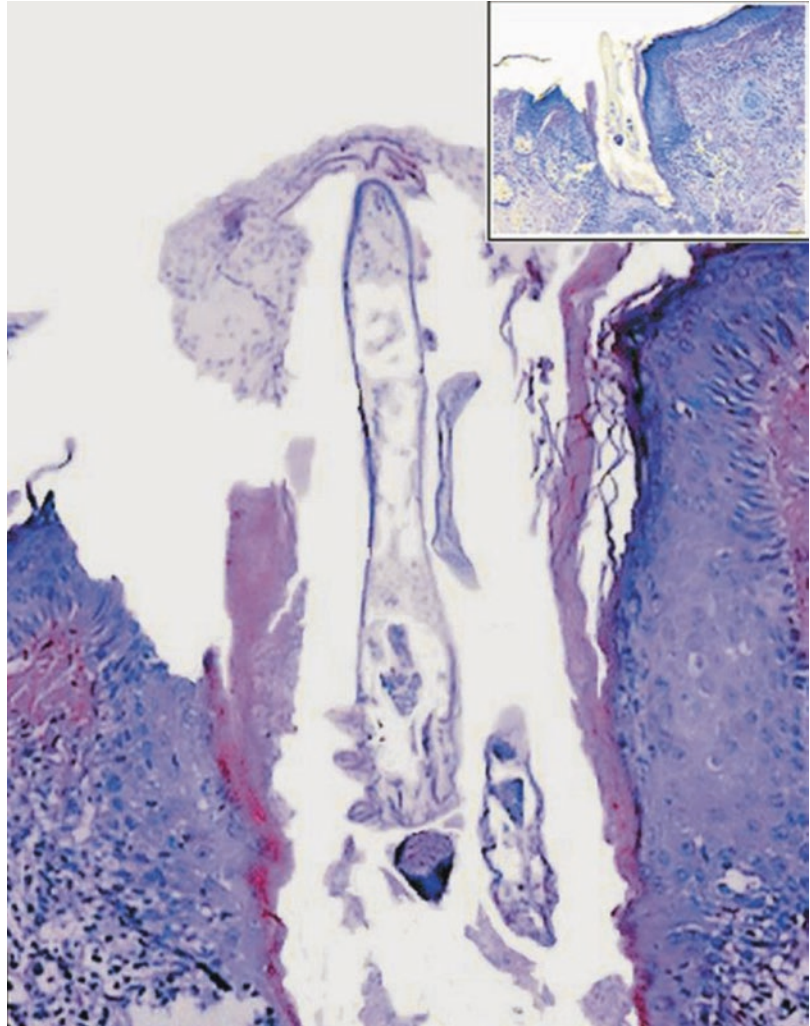
PPR	Acne
	Periorificial dermatitis
	Bacterial folliculitis
	Demodicidosis
	Iododerma
	Bromoderma
Granulomatous variant PR	Sarcoidosis, periorificial dermatitis
	Leprosy
	Lymphoma
	Leukemia cutis
	Mycosis
OR	Viral conjunctivitis
	Bacterial conjunctivitis
	Seborrheic blepharitis
	Glaucoma

Therapeutic Approach

To date rosacea remains an incurable disease, albeit treatable and controllable. Despite rosacea being a relatively benign disease there is significant morbidity associated with it in terms of the impact on the patient's quality of life and psychological well-being [80]. It is important to conduct a detailed anamnesis and to use some time during the medical appointment to calm down the patient regarding the benign nature of the condition, to explain the disease, to try to identify the triggering factors (e.g., alcohol, heat, cold, physical and psychological stress), and to discuss the treatment aims. Such an approach may improve the

physician–patient relationship and the patient's quality of life [80–82].

The skin condition can be improved and preserved through a wide range of treatments. Treatment aims are:

1. To alleviate signs and symptoms, such as skin irritation or redness, and to decrease papules and pustules
2. To retard or prevent the development of milder and more severe disease presentations
3. To make remissions easier and avoid flares
4. To keep the best skin condition possible
5. To improve the patient's quality of life

The rosacea care triad, which emphasizes patient education on the condition, skin care, and treatment, offers a wide approach to deal with all patient needs and not only the disease's specific signs and symptoms. In ETR, for example, techniques such as relaxation, cognitive-behavioral psychotherapy, biofeedback, or drugs such as antidepressants or β-adrenergic blockers, can be used to deal with the emotional triggers whenever they play a significant role [83].

As regards skin care, the patient must be educated to wash gently, and to use sunscreen with an SPF of 30 at least (decreasing ROS) and moisturizers when necessary [84]. Because the skin of these patients is more sensitive it is sometimes difficult to find the optimum tolerated sunscreen lotion and moisturizer, but symptom improvement and remission prevention are crucial [82].

A revision of the 2015 Cochrane analysis, which included 106 research studies encompassing 13,631 participants, had its conclusions classified into evidence levels of high, moderate, low, and very low quality according to the GRADE (Box 22.4) [85].

Box 22.4 Options to treat rosacea according to the GRADE

	Evidence – GRADE[a]		
	High	Moderate	Low
Topical	Azelaic acid	Metronidazole	Cyclosporine ophthalmic emulsion
	Ivermectin		
	Brimonidine		

	Evidence – GRADE[a]		
	High	Moderate	Low
Systemic	Doxycycline	Tetracycline	Minocycline
	Isotretinoin		Azithromycin
Others			Pulsed dye laser
			Intense pulsed light

[a]*GRADE* Grading of Recommendations Assessment, Development, and Evaluation

Treatment Methods (Box 22.5)

Topical Treatments

High GRADE evidence levels

- *Azelaic acid*: antimicrobial, anti-inflammatory (ROS decrease), and antikeratinous properties [86]; it can reduce KLK5 and cathelicidin expression [87]. Available in gel at a 15% concentration or in cream at a 20% concentration; it can be used twice a day for PPR over 6–8 weeks.
- *Ivermectin*: antiparasitic properties (*D. folliculorum*). Available in 1% cream; it can be used once a day for PPR over 6–8 weeks.
- *Brimonidine*: α2-adrenergic agonist. Available in 0.33% gel, it can be used once a day for RET; it has a 12-h vasoconstrictive effect. Contraindications: heart failure, obliterans thromboangiitis, Raynaud's disease, postural hypotension, Sjögren's disease, scleroderma.

Moderate GRADE evidence levels

- *Metronidazole*: imidazolic antibiotic, with anti-inflammatory properties (ROS decrease). Available in cream or gel at 0.75% or 1%; it can be used once or twice a day for PPR.
- *Other topical treatments*: Clindamycin at 1% and erythromycin at 2%, isolated or combined with 5% benzoyl peroxide, 10% sodium sulfacetamide/5% sulfur emollient foam, 5% permethrin, tretinoin. Cyclosporine ophthalmic emulsion for ocular rosacea.

Systemic Treatment

High GRADE evidence levels

- *Doxycycline*: the main treatment for PPR, it is an antibiotic of the tetracycline class with

anti-inflammatory properties (decreased expression of metalloproteinases, infraregulation of inflammatory cytokines, decreased levels of ROS [88]). Available in 40-mg doses (30 mg of immediate release and 10 mg of slow release, still not available in many countries), and in a 100-mg dose. The 40-mg dose can be used as one tablet per day, preferably 1 h before meals or 2 h after meals. In case the 100-mg dose is the only one available, half of the tablet can be used a day or one tablet every other day. It is recommended that treatment continues for 6–8 weeks followed by a new patient evaluation. After 8 weeks of doxycycline treatment the patient displays excellent reaction of the inflammatory presentation, including partial improvement of the erythema (Fig. 22.7).

- *Isotretinoin*: Can be used for severe or resistant cases of PPR; it decreases TLR2 expression. The recommended dose is 0.3 mg/kg a day over 12 weeks. Available in 10-mg and 20-mg doses. Absolutely contraindicated for pregnant women.

Moderate GRADE evidence levels

- *Tetracycline*: anti-inflammatory properties (decreased metalloproteinase expression, inflammatory cytokine infraregulation, decreased ROS levels). Available in 500-mg tablets; it can be used in a 500–1,000 mg/day dose.

Other systemic treatments

PPR: minocycline, azithromycin, sulfamethoxazole/trimethoprim, erythromycin, metronidazole, lymecycline, ivermectin, dapsone.

ETR: carvedilol. The patient's heart rate and blood pressure must be controlled.

Laser and Light Treatment

These types of treatment basically act on the vascular component by decreasing telangiectasias and basal erythema. The more often used treatments include intense pulse light (IPL), pulsed dye laser, and KTP and Nd:YAG laser. The phymatous component of rosacea can be treated with an ablative laser, such as the CO_2, Er:YAG, Nd:YAG laser.
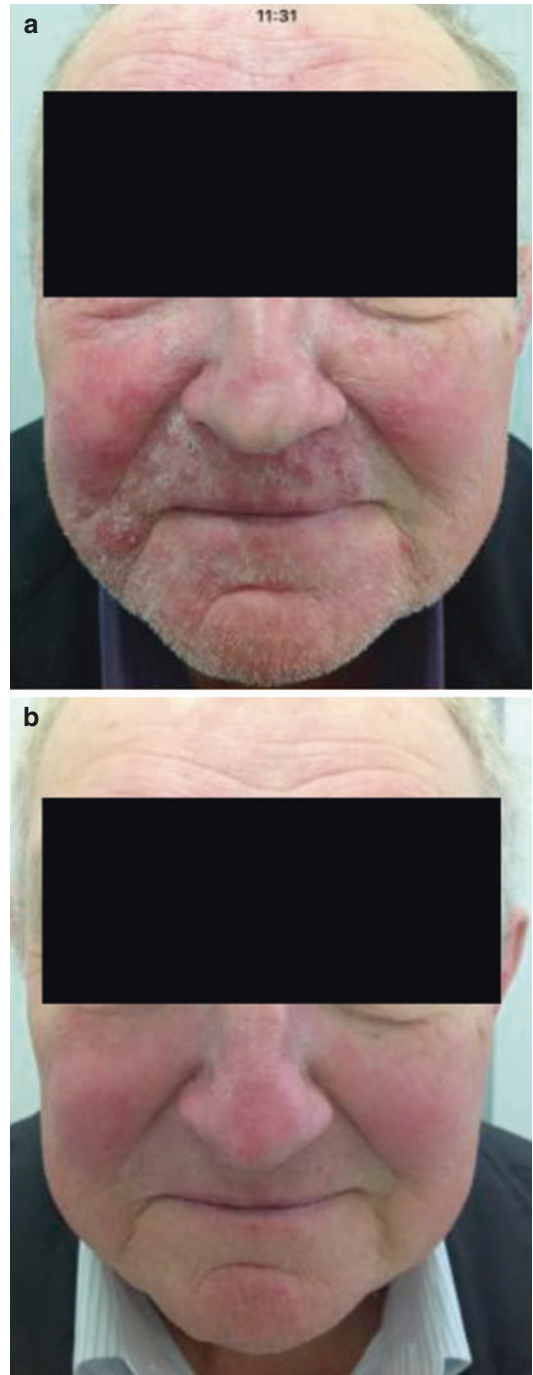
Fig. 22.7 (**a**) before doxycycline treatment; (**b**) after doxycycline treatment. Therapeutic effect of doxycycline

Surgical Treatment

Particularly used for phyma correction. Electrosurgery is an elective surgery, but trichloroacetic acid may be used.

> **Box 22.5 Rosacea treatment: synthesis of the main drug options, according to clinical subtype**
>
> *Rosacea*
>
> Erythematous telangiectatic: brimonidine topical, oral carvedilol, and LIP
>
> Papular-pustular: oral doxycycline, topical ivermectin, topical azelaic acid, and topical metronidazole
>
> Phymatous: inflammation reduction with isotretinoin or doxycycline after electrosurgery or ablative laser
>
> Ocular: doxycycline, topical cyclosporine
>
> Granulomatous: isotretinoin, doxycycline, dapsone

Glossary

Cathelicidin Antimicrobial peptides found in the mammalian tissue induced by injury or inflammation. They belong to the immune system and work as activators and controllers of immune reactions.

Flushing The most common symptom of rosacea, characterized by a transient facial blush or redness. The skin can be lightly rose as if blushed, or it may seem slightly sunburned. Sufferers may refer to itching or pricking during rosacea flares.

GRADE (Grading of Recommendations Assessment, Development, and Evaluation) System developed by a group of collaborative researchers aiming at the creation of a universal, transparent, and sensitive system to grade the quality of scientific evidence and recommendation power. The GRADE system classifies evidence quality (reliability of the used information) at four levels: high (powerful reliability of the real effect is near the assessed one), moderate (moderate reliability of the assessed effect), low (limited effect reliability), and very low (very limited reliability of the effect assessment). There is a significant uncertainty degree in the findings. Evidence from randomized clinical trials begins with high evidence level; evidence from observational studies begins with low evidence level.

Kallikrein A polypeptide of proteolytic reaction which acts upon protein substrates of varied nature. Kallikrein has a vasodilating direct action, but also an indirect one because of its proteolytic feature.

Metalloproteinases An important group of zinc-dependent proteolytic enzymes (endopeptidases) that account for the degradation of the extracellular matrix and the basal membranes. The metalloproteinases degrade the matrix macromolecules including interstitial collagen, fibronectin, lamina, and proteoglycan, among others. The expression of many metalloproteinases is increased in the skin of rosacea patients.

Photodamage Represented by clinical changes resulting from acute or chronic events determined by biochemical and molecular processes caused by ultraviolet radiation exposure.

Phyma A rosacea phase determined by sebaceous gland hyperplasia, initially showing erythema, edema, and follicular orifice dilation, followed by the development of fibrous tissue. This process can affect the nose (rhinophyma), the mentum/chin (gnatophyma), the forehead (metophyma), the ears (otophyma), and the eyelids (blepharophyma).

Transcriptome The transcriptome corresponds to the genetic code fraction (DNA) transcribed by the RNA polymerase into the RNA molecules, that is, an organ, tissue, or cell lineage's total set of transcripts (RNA messengers, ribosomal RNAs, transporter RNAs, and microRNAs).

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Vitiligo

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Key Points Summary
- Vitiligo is a highly prevalent chronic systemic disease whose major burden is the impact on patients' self-esteem
- Vitiligo is a neglected disease for which as yet there is no FDA-approved treatment
- Topical corticosteroids are considered a safe first-line treatment option. Head and neck lesions tend to have a better response
- Narrow-band ultraviolet B phototherapy is considered the first line of treatment for generalized vitiligo
- Surgical treatment is an excellent option for patients with stable disease who have failed to respond to previous clinical treatments

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Epidemiology

Vitiligo affects individuals worldwide, with prevalence ranging from 0.093% in China to 1.8% in India, according to different endemic settings [1, 2]. No age or gender effect has been reported for vitiligo. The mean age at onset for common vitiligo was estimated as 22.4 years for Caucasians from the United States/Canada and 23.9 years in a mixed population from Brazil [3, 4]. Brazil has no up-to-date epidemiologic data on the incidence and prevalence of vitiligo.

An increased incidence of nonmelanoma cancer and actinic keratoses would be expected in patients with vitiligo because of the lack of melanocytes. However, three recent studies failed to detect a correlation between vitiligo and nonmelanoma skin cancer and melanoma skin cancers in comparison with the general population. In three large studies, the incidence of melanoma and nonmelanoma skin cancers was markedly reduced in vitiligo patients. Teulings et al. [5] did not observe a trend of increasing prevalence of these skin cancers in the subgroup of patients treated with psoralen plus ultraviolet A (PUVA) and narrow-band ultraviolet B (UVB). The study was adjusted for age and time of exposure during life. By contrast, in an independent cohort study Paradisi et al. [6] found a higher risk of both skin cancer groups in patients who underwent phototherapy.

Experimental data have led some authors to hypothesize that the low incidence of skin cancer

in vitiligo might be due to an overexpression of the p53 protein, which has an anticancer effect. Immunohistochemical studies have demonstrated an increased expression of p53 in both affected and normal skin of vitiligo patients compared with the skin of controls with a history of basal cell carcinoma [7, 8]. Furthermore, the reduced expression of GD3, a member of the keratinocyte apoptosis pathway, induces a compensatory mechanism of epidermal thickening to protect the affected skin from ultraviolet radiation damage [9]. Of note, the major alleles of a single nucleotide polymorphism in the *TYR* vicinity have been shown to be associated with vitiligo. The *TYR* gene encodes for a tyrosinase, an enzyme involved in melanin synthesis, and constitutes a major autoantigen in common vitiligo. The minor allele of the same TYR single nucleotide polymorphism associated with vitiligo was shown in association with susceptibility to malignant melanoma. The inversion of the risk allele between vitiligo and malignant carcinoma suggest that TYR mediates different or perhaps even inverse biological mechanisms in these two diseases. Hence, an increased immune surveillance for melanoma is a possible role for TYR in vitiligo [10, 11]. A final explanation to elucidate the reduced incidence of skin cancer in patients with vitiligo is that patients had probably been instructed to use sunscreen lotion in consultation with dermatologists.

Etiopathogenesis

The etiopathogenesis of vitiligo has not been fully elucidated, and several theories have been proposed. Among these, the autoimmune hypothesis is currently the most accepted by experts [12]. In addition to this theory, others have been intensively studied, such as the epidermal adhesion defect and biochemical and neural hypotheses. Some groups have been trying to propose models that integrate the oxidative, neural, genetic, and immune theories [13]. However, the same causal mechanisms might not apply to all cases, and different pathogenetic mechanisms might work together, leading to the same clinical result [14]. Here we discuss the melanocyte and keratinocyte adhesion defect, and autoimmune and biochemical theories.

Autoimmune Theory

The leading pathophysiologic hypothesis to explain melanocyte disappearance in vitiligo is related to a primarily immune-mediated inflammatory reaction targeting melanocytes destroyed by antigen-specific T cells. IT is known that autoreactive cytotoxic T cells are both necessary and sufficient to cause the disease in human skin [15]. These antigenic proteins in vitiligo have been identified, and include gp100, MART1, tyrosinase, and tyrosinase related proteins 1 and 2 [16].

Some studies in animals support the role of the innate immune response, and vitiligo is likely to have a second stage whereby the innate immune system subsequently triggers the adaptive immune system by activating dendritic cells, thereby facilitating targeted autoimmune destruction of melanocytes [14]. In addition to the antigen specificity of adaptive immunity, the innate immune system can rapidly initiate responses without specific antigen recognition, and does so through activation of pattern recognition receptors (i.e., Toll-like receptors), by damage-associated molecular patterns (i.e., reactive oxygen species), inducing melanocyte stress and inflammation initiation [16].

The initial perception that autoimmunity was involved in patients with common vitiligo was based on the frequent co-occurrence of autoimmune diseases in these patients and their relatives, in addition to the favorable response to immunosuppressive therapies such as photochemotherapy with UVA and topical and oral corticosteroids [17–20].

Thyroid diseases are the most common comorbidities in common vitiligo, and a recent systematic review of thyroid diseases in patients with vitiligo identified average prevalence rates of thyroid diseases, autoimmune thyroid diseases, and the presence of thyroid-specific autoantibodies as 15.1%, 14.3%, and 20.8%, respectively. However,

several autoimmune diseases, such as psoriasis, alopecia areata, and type 1 diabetes, have been associated with vitiligo [4].

Some studies have stated that vitiligo is accompanied by abnormal humoral immunity, and high levels of serum circulating autoantibodies have been detected in 5–10% of patients, predominantly of the immunoglobulin G class and particularly antityrosinase 1 and 2 (TRP-1 and TRP-2). However, the role of antimelanocyte antibodies in vitiligo pathogenesis remains uncertain, and it has been suggested that their presence may be secondary to keratinocyte and melanocyte damage, a hypothesis that has been put forward in the past [12]. Melanocytes are capable of presenting antigens in the presence of major histocompatibility complex (MHC) class II, which would allow HLA-DR+ cells present in the perilesional vitiligo area to present antigens in response to trauma or local inflammation, in the latter case leading to autoimmune destruction of melanocytes [21]. Several studies have demonstrated the presence CD8+ lymphocytic infiltrates at the dermo-epidermal junction in perilesional vitiligo skin [21, 22]. It has been observed experimentally that in some patients with common vitiligo there was infiltration of CLA+ T cells in the perilesional skin, raising the possibility that the recruitment of these T cells occurred through dendritic cell activation, which in turn are activated at the epidermal trauma region [23]. Mice with surgically excised melanoma tumors generated cytotoxic T-lymphocyte memory response against melanocytes. These mice that lacked regulatory T cells (TREGs) developed vitiligo, suggesting that TREGs would prevent autoimmunity against melanocytes [24]. There are several reports implicating TREGS to be dysregulated in patients with vitiligo, although there is no clear consensus on specific abnormalities (i.e., decreased numbers, skin homing defects, or functional defects) [16].

Evidence has also been found even in segmental vitiligo, whose pathogenesis was primarily linked to sympathetic nerve dysfunction and mosaicism, that immune-mediated cellular responses including CD8+ T lymphocytes is involved in the early stages of this type of disease [25].

Adhesion Defect Theory

It has been suggested that adhesion defects are involved in the disappearance of melanocytes in vitiligo lesions [26]. The main clinical sign reinforcing this theory is the occurrence of koebnerization or Koebner phenomenon (appearance of vitiligo after an acute or chronic trauma), which may be present in up to 31% of Caucasian patients with common vitiligo [4]. This observation led to the proposal of a new theory that nonsegmental vitiligo is a melanocytorrhagic primary disorder, i.e., an acute loss of melanocytes would probably occur (because most patients have a sudden onset of lesions), with an altered response of melanocytes to friction and possibly other types of stress, which would induce cell detachment and subsequent transepidermal loss. In this context, the authors of this theory speculated that an autoimmune phenomenon might be triggered by antigen release and recognition of affected melanocytes by dendritic cells or memory T cells during transepidermal migration, thereby exacerbating the detachment and loss of more melanocytes [13].

Alterations in the main protein that adheres melanocytes to the epidermis basal layer, DDR1 (Discoidin Domain Receptor 1), have been implicated as one of the aggravating factors in the loss of melanocytes. Initially, genetic association studies found evidence of a connection between nonsegmental vitiligo and DDR1 gene alleles, which was more evident in vitiligo patients with the onset of disease before 25 years of age [27]. Functional studies attempting to explain the involvement of DDR1 and CCN3 protein (which controls the adhesion of DDR1 to epidermis basal layer) observed that perilesional melanocytes did not express CCN3; moreover, the silencing of CCN3 in melanocytes induced a significant inhibition of their adhesion to collagen IV [26, 28]. In this same study, it was demonstrated that the expression of DDR1 in lesional skin was decreased compared with perilesional skin in most patients, and collagen IV expression was diminished in all affected individuals [26]. Along this same research line, two studies confirmed the decreased expression of DDR1 in lesional

epidermis, whereas epidermal expression of DDR1 was secondary only to expression in keratinocytes and not in the basal layer of epidermis, where melanocytes are located. Reichert-Faria et al. hypothesized that the vitiligo is a condition whereby all of the epidermis is affected and not only melanocytes [29]. DDR1 has a role in the impairment of melanocyte adhesion process in vitiligo [30]. Tarlé et al. has recently revealed that alleles of marker rs10431924 of the CDH1 gene are associated with vitiligo, especially in the presence of autoimmune comorbidities [31]. Loss or a dysfunctional E-cadherin could result in morphologic and functional impaired melanocytes and possibly initiate a cascade of immune response and oxidative stress feeding back the process of melanocyte detachment. A recent functional study showed that E-cadherin is absent from or discontinuously distributed across melanocyte membranes of vitiligo patients long before clinical lesions appear. This abnormality is associated with the detachment of the melanocytes from the basal to the suprabasal layers in the epidermis. Using human epidermal reconstructed skin and mouse models with normal or defective E-cadherin expression in melanocytes, the authors demonstrated that E-cadherin is required for melanocyte adhesiveness to the basal layer under oxidative and mechanical stress [32].

Biochemical Theory

The hypothesis that vitiligo could be caused by a metabolic pathway dysfunction, not necessarily related to melanocytes, which would lead to the production of toxic metabolites such as catecholamines, quinones, and reactive oxygen species, has been widely investigated [12, 33]. Several studies report that cellular stress pathways are dysregulated in melanocytes from vitiligo patients, suggesting that melanocyte-intrinsic defects participate in disease pathogenesis [16].

The involvement of oxidative stress damage to melanocytes is supported by evidence suggesting an imbalance between the pro-oxidant/ antioxidant systems in the epidermis of patients with vitiligo. There is an increased sensitivity of melanocytes to oxidative stress [34, 35] and

it has been demonstrated that melanocytes on the lesion borders of vitiligo patients showed increased sensitivity to oxidative stress when in culture [34]. This finding has been attributed to an inherited inability to manage stressors from normal cellular processes (e.g., melanogenesis) or exposure to environmental factors (injury or chemicals: monobenzone and other phenols). In response to stressors, reactive oxygen species are released from melanocytes, initiating a cascade of events with subsequent activation of innate immune cells [14]. Patients with vitiligo have a low level/activity of enzymatic and nonenzymatic antioxidants such as catalase, glutathione peroxidase, and vitamin E, possibly increasing H_2O_2 toxicity [35, 36] and catalase is the principal enzyme implicated in H_2O_2 removal, which is important in the management of oxidative stress. Studies have reported the involvement of the adrenergic and cholinergic systems in vitiligo pathogenesis. It has been demonstrated that high concentration of H_2O_2 inhibits the activity of cholinergic enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) by oxidation of amino acid residues in the active sites of these enzymes [37, 38]. AChE is an important enzyme in promoting and maintaining oxidative stress, and interestingly, AChE activity is low in vitiligo skin lesions during depigmentation, but returns to normal when the damaged skin starts repigmentation [37].

Vitiligo Genetics

A diverse set of analytical approaches indicates that environmental factors alone are not sufficient to explain human susceptibility to vitiligo. Evidence from observational studies including familial aggregation of cases [39, 40], complex segregation analysis (CSA) [49–51] and twin studies [3] support a genetic component contributing to vitiligo pathogenesis. Using genetic epidemiology approaches such as genome-wide linkage studies (GWLS), genome-wide association studies (GWAS), and candidate-gene based studies, researchers identified genes and genomic loci modulating the outcome of vitiligo. While such techniques have helped to unravel key

aspects of disease pathogenesis (i.e., distinct set of genetic factors controlling vitiligo associated with autoimmune diseases or the involvement of melanocyte adhesion and melanin biosynthesis in vitiligo pathogenesis), they did not explain the totality of the heritability reported by observational studies.

Observational Studies in Vitiligo

The familial clustering of cases and the segregation of disease in a non-Mendelian pattern set vitiligo as a complex multifactorial disease of polygenic inheritance [39, 40]. A study with 194 families, mainly Caucasian from the United States, indicates that 20% of the vitiligo cases had at least one first-degree relative affected by disease [3, 40]. The relative risk for an offspring of a vitiligo case to develop disease was 36-fold higher than that expected for the general population [40]. Sibship and parenthood of vitiligo cases present a 12-fold and 7-fold increase, respectively, for the risk to develop vitiligo in comparison with the general population [40]. An independent study with 2,624 vitiligo probands from the United States and United Kingdom observed 7% of first-degree relatives of index cases being affected by vitiligo and an 18-fold increased risk than the general population [3]. CSAs support the existence of a genetic component cosegregating within families containing vitiligo cases; however, there is no consensus regarding the inheritance model [40–42]. Phenotypic concordance of vitiligo in pairs of monozygotic (MZ) twins and the absence of concordance in pairs of dizygotic (DZ) twins provides additional evidence for a genetic component in vitiligo. A study assessing 46 pairs of twins showed that among 22 pairs of MZ twins the concordance for vitiligo was 23% while in none of the 24 pairs of DZ twins the second sib presented the disease [3].

Genome-wide Linkage Studies to Discover Genes in Vitiligo

GWLS are hypothesis-free approaches that evaluate the nonrandom transmission of genomic regions among affected individuals in a family-based design. A series of GWLS identified multiple loci likely harboring vitiligo susceptibility genes. Hitherto, positional cloning of these linkage regions resulted in only a few candidate genes associated with disease. The first GWLS in vitiligo have shown the chromosome 17p13 linked to the comorbidity of vitiligo and systemic lupus erythematosus (SLE) in a small sample set of 16 families (Figs. 23.1) [43]. An independent study with 102 families confirmed the linkage of the 17q13 region with vitiligo associated with autoimmune diseases [44]. Positional cloning of the 17p13 region identified polymorphisms near the *NLRP1* gene in association with vitiligo as the probable origin of the linkage [45, 46]. The role of NLP1 in vitiligo and in autoimmune diseases is likely due to an upregulation of interleukin (IL)-1β processing via the NLRP1 inflammasome [47]. This mechanism is dependent of a haplotype combination of multiples coding variants associated with risk to vitiligo [47].

The chromosome 22q12 was suggestively linked to vitiligo pathogenesis by two independent GWLS in Caucasians and in Asian populations, respectively (Fig. 23.1) [44, 48]. An expansion of the study in the Asian population to 143 Chinese multiplex families confirmed the linkage with vitiligo on chromosome 22q12 [49]. Fine-mapping of the 22q12 locus identified variants near the *XBP1* gene in association with vitiligo in independent populations [50, 51]. The alleles associated with risk for vitiligo are prone to a higher transcriptional activity of the *XBP1* gene in patients' injured skin [51]. The *XBP1* gene encodes a transcription factor that regulates expression of MHC class II genes and loci frequently associated with autoimmune diseases [52]. Interestingly, the GWLS in the Asian population identified a suggestive linkage for vitiligo on chromosome 6p21–p22, a region where the MHC complex is located [49].

The MHC complex on chromosome 6p21 was observed in linkage with vitiligo in ethnic independent populations from China, Brazil, and Colombia (Fig. 23.1) [53]. Variants near human leukocyte antigen (HLA) class I and
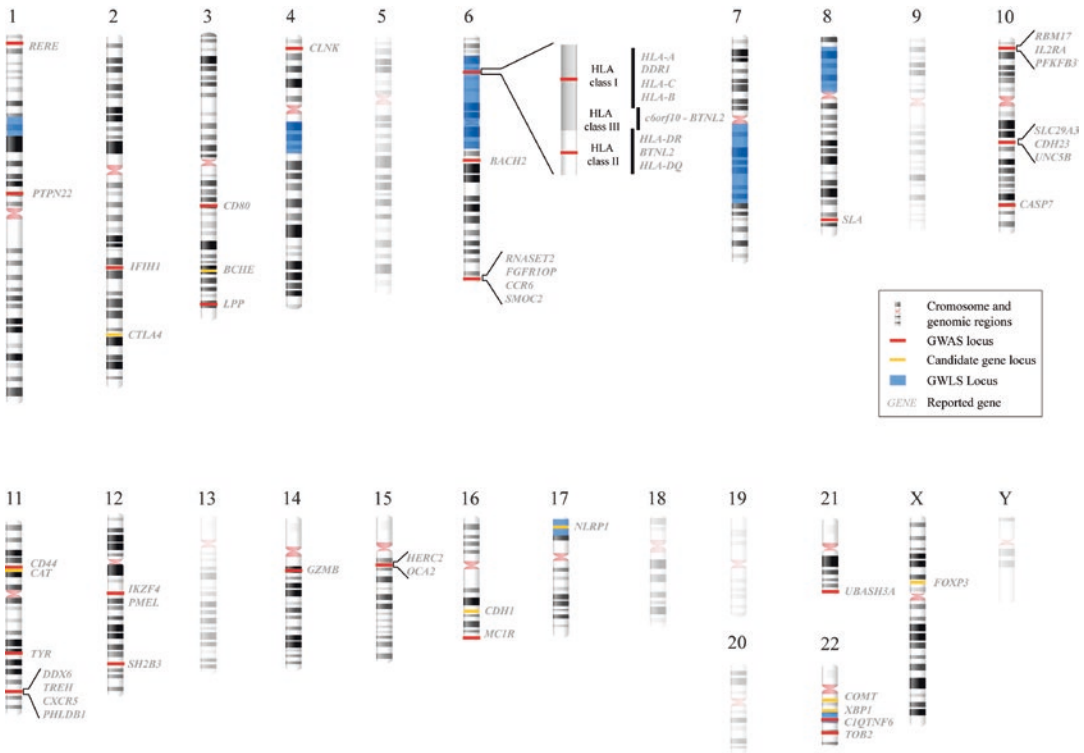
Fig. 23.1 Ideogram presenting genomic regions and genes linked or associated with vitiligo pathogenesis. A summary of genes and genomic regions consistently associated or linked to vitiligo pathogenesis are pointed out according to their genomic location in the 22 autosomes or the sexual chromosomes

HLA class II genes have been consistently implicated in vitiligo pathogenesis [54, 55]. Recent studies denoted a biological function for HLA variants associated with vitiligo [56, 57]. For instance, homozygotes for a vitiligo-risk haplotype located between the *HLA-DRB1* and *HLA-DQA1* genes presented an increased surface expression of HLA-DR and HLA-DQ in monocytes [56]. In peripheral blood mononuclear cells, a vitiligo-risk haplotype near the *HLA-A* gene increases the expression of *HLA-A*02:01* allele by 39% in comparison with the non-risk haplotype [57].

Additional signals of linkage were reported for vitiligo phenotypes; however, no additional candidate genes have emerged from the reported regions. A locus on chromosome 1p31.3–p32.2 was linked to the comorbidity of vitiligo and Hashimoto thyroiditis in one large kindred (Fig. 23.1) [58]. The 1p31.3 region was suggestively linked to vitiligo when 70 independent families were evaluated [59].

An 89.4 cM region on chromosome 7 and a 54.2 cM region on chromosome 8 were linked to vitiligo pathogenesis in 102 families from United Kingdom and United States (Fig. 23.1) [51]. The signal on chromosome 7 derived from vitiligo associated with autoimmune diseases, while in chromosome 8 the linkage was mainly in families without comorbidities [51]. A GWLS in 106 Chinese families reported the chromosome 4q13–q21 linked to vitiligo (Fig. 23.1) [48]. Moreover, a moderate linkage peak for vitiligo was observed on chromosome 1p36. Interestingly, a GWAS approach described variants near the *RERE* gene on chromosome 1p36 associated with risk factors for vitiligo [10].

Genome-wide Association Studies to Discover Genes in Vitiligo

GWAS assess a dense set of genetic variants located across the entire genome for association

with a trait of interest [60]. Population-based GWAS compare the differences in genotype frequencies on cases versus controls using large cohorts. Multiple studies have used the aforementioned approach in the study of the genetic basis of vitiligo pathogenesis.

A population-based GWAS compared 1,514 generalized vitiligo cases and 2,813 health controls [10]. In total, ten independent loci were associated with generalized vitiligo in Caucasians (Fig. 23.2) [10]. The loci reported by the GWAS were independent of comorbidities being significant in the presence or absence of other autoimmune diseases [10]. The exception was the association of variants near the *PTPN22* gene, which were solely observed for vitiligo concomitant with other autoimmune diseases. The *PTPN22* gene is known to be associated with autoimmune related diseases such as rheumatoid arthritis and SLE [61, 62]. In the non-HLA region, variants next to the *TYR* gene were a notable association with vitiligo [10]. *TYR* encodes an enzyme of the melanocyte that is involved in melanin biosynthesis [63]. Mutations impairing *TYR* causes oculocutaneous albinism, a group of diseases characterized by lack of melanin in skin, hair, and eyes [64]. A meta-analysis combining the GWAS in Caucasians with a second GWAS study in a total of 3,187 vitiligo cases and 6,723 controls reported 13 additional new loci associated with vitiligo (Fig. 23.1) [65]. When the Caucasian population from the first GWAS in vitiligo was stratified according to age

at disease onset, only the signal near the *C6orf10-BTNL2* gene was associated with early onset of disease [66].

A population-based GWAS in Chinese subjects containing 1,117 vitiligo cases and 1,429 healthy controls reported a strong association of the HLA region with vitiligo [67]. A second signal of association was observed in a region near the tip of chromosome 6 long arm where multiple candidate genes were located (Fig. 23.1) [67]. An expansion of the study in the Chinese population to 6,857 vitiligo cases and 12,025 controls described an additional three loci associated with disease (Fig. 23.1) [68]. The study also validated three loci associated with vitiligo in the Caucasian population where the *LPP*, *IL2RA*, and *C1QTNF6* genes were located [68].

Mechanistic Candidate Genes in Vitiligo

The candidate gene approach studies gene(s) that are central in key biological processes related to disease pathogenesis. Difference mechanisms were proposed for the etiopathogenesis of vitiligo. Among those supported by biological findings are autoimmunity, defect in melanocyte adhesion, and biochemical metabolic dysfunction [53].

Different hypotheses were proposed for the autoimmunity in vitiligo, such as the production of autoantibodies, loss of self-tolerance magnifying the cytotoxicity of lymphocytes against melanocytes, depletion of regulatory T cells in the skin of affected individuals, and a few other that were further described by Tarle et al. [53]. One hypothesis worth mentioning is the melanocytes' capability to present antigens through MHC after trauma or inflammation [21]. Among the most documented associations with vitiligo are variants with biological impact in the MHC gene such as *HLA-A*, *HLA-DRB1*, *HLA-DQA1*, and HLA class II regulator *XBP1*. It is reasonable to think that some of these variants may contribute to a pathologic inflammatory response directly against melanocytes via a boost in antigen presentation [56, 57].

Fig. 23.2 Segmental vitiligo

It has been proposed that adhesion defects are connected with the disappearance of melanocytes in vitiligo lesions [26]. The defect of melanocyte attachment hypothesis originated from clinical observations of the Koebner phenomenon, an event that affects up to 30% of Caucasian patients with vitiligo [69]. The Koebner phenomenon is characterized by the appearance of vitiligo-like lesions after an acute or chronic trauma. A study of generalized vitiligo cases reported melanocyte detachment after mechanical friction of patient's unaffected skin; the same was not observed in a control group [70]. The *DDR1* gene encodes a transmembrane tyrosine kinase receptor that is the main adhesion protein for melanocyte to the basal membrane via the integrin CCN3 [26]. Lesioned skin of vitiligo patients had lower transcription levels of *DDR1* in comparison with unaffected skin [29]. A family-based association study with 225 families from Brazil reported the association of vitiligo and variants near the *DDR1* gene [27]. The association of *DDR1* and vitiligo was replicated in population-based case-controls in Brazilians and Koreans [27, 71]. The DDR1 forms a complex with the cell-surface E-cadherin that is important for the maintenance of apical junction complexes and epithelial polarity [72]. Variants near *CDH1* gene encoding E-cadherin were associated with vitiligo in Brazilians [31]. The *CDH1* association was particularly stronger in vitiligo associated with autoimmune diseases [31]. Other genes involved in the melanocyte adhesion remain to be studied.

The biochemical metabolic dysfunction hypothesis has been extensively debated [12]. The involvement of oxidative stress leading to a toxic damage to the melanocytes was observed by in vivo experiments showing the accumulation of H_2O_2 in the epidermis of vitiligo patients [73]. The accumulation of H_2O_2 in the epidermis inhibits the activity of cholinergic enzymes BChE [38]. Studies have shown that the epidermal expression of *BCHE* was lower in vitiligo lesions in comparison with healthy skin [37, 38]. Variant near the *BCHE* gene were associated with vitiligo in two independent population samples from Brazil [74]. The vitiligo risk alleles near the *BCHE* gene correlated with a higher enzymatic activity of BChE in plasma [74].

Clinical Presentation

Vitiligo is an acquired chronic systemic disease [53]. It is depicted as a pigmentary disorder of noncontagious etiology. Vitiligo lesions are characterized by achromic or hypochromic macules or patches on the skin, mucous membranes, and hair, resulting from progressive disappearance of melanocytes in affected areas. These lesions appear in different shapes and sizes and may arise in any area of the tegument [53]. Vitiligo is the most common depigmenting disorder, and at least 20% of patients report pruritus and affected areas are more susceptible to burns with sun exposure [75].

Clinical aspects in vitiligo suggest systemic involvement in the disease. Melanocytes in the uveal ocular tract and in the vascular system and modiolus of the cochlea in the auditory apparatus can also suffer damage during the course of disease. Previous studies detected hypopigmented spots on the iris and comorbidities such as uveitis and sensorineural hypoacusis in 16% of patients with vitiligo [76–78]. Despite of the visual aspect of depigmentation, a major burden in vitiligo is the impact on the patient's self-esteem. The consequences can range from severe depression, especially in children, to anxiety, which diminish the quality of life of patients [79, 80].

Classification

The Vitiligo Global Issues Consensus Conference, an international group of experts on vitiligo[81] – held between 2011 and 2012, classified vitiligo in the following clinical forms (Table 23.1)

- Non-segmental vitiligo (NSV): a group that comprises acrofacial, mucosal, generalized or common, universal, and mixed forms, besides some rare forms. The vitiligo lesions usually have a bilaterally distribution and may evolve over time.

(a) Acrofacial: it can affect, face, head, hands, and feet, and preferably involves the perioral

region and the extremities of digits; this form can later progress to the generalized or universal form [14].

(b) Mucosal: affects the oral and genital mucosae. Furthermore, areas of mucosa may also be affected in patients with acrofacial, common, or universal forms; when it involves only one mucosal site it is classified as indeterminate.

(c) Generalized or common (Fig. 23.3): Macules/patches are often symmetric; it can affect any part of the tegument, mainly hands, fingers, face, and trauma-exposed areas. It has a predilection for extensor than flexural surfaces.

(d) Universal: is the form that affects the largest extent of tegument (80–90% of body surface), and is the most common form in adulthood. The generalized or common form usually precedes it.

(e) Mixed: The coexistent involvement of segmental and nonsegmental vitiligo. Most often, the segmental form precedes NSV.

(f) Rare forms: vitiligo punctata, minor (an incomplete defect in pigmentation, with a pale skin color, mainly in dark skinned individuals), and follicular. These types were considered as unclassifiable.

- Segmental vitiligo: This type is characterized by their uni-, bi-, or multiple segments or band-shaped distribution (Fig. 23.4). The unisegmental form is the most common one and consists of one or more white macules on one side of the body, usually respecting the body midline, and there is also involvement of body hair (leukotrichia) besides rapid onset of the condition. Less commonly, it can affect two or more segments and even have bilateral segmental distribution, starting simultaneously or not. Early involvement of the follicular melanocyte reservoir and rapid stabilization occur. Disease onset occurs at an early age [14].

- Unclassifiable forms or undetermined vitiligo

Table 23.1 Vitiligo Global Issues Consensus Conference: classification

Types	Subtypes
Vitiligo/nonsegmentary vitiligo	Acrofacial
	Mucosal (more than one mucosal site)
	Generalized or common
	Universal
	Mixed (associated with segmental vitiligo)
	Rare variants
Segmental	Uni-, bi-, or plurisegmental
Unclassified/undetermined	Focal
	Mucosal (one site in isolation)

Fig. 23.3 Generalized or common vitiligo

Fig. 23.4 Perifollicular pattern of repigmentation is commonly seen after phototherapy

(a) Focal: small, isolated white macules without segmental distribution that have not evolved into segmental or non-segmental vitiligo forms after 1–2 years.

(b) Mucosal: when only one mucosa site is affected.

Association with Other Diseases

Vitiligo may be associated with several autoimmune diseases. Most patients, however, are otherwise healthy. Generalized vitiligo is more likely to be associated with other autoimmune diseases than segmental vitiligo, especially in patients with a family history of vitiligo or other forms of autoimmunity [82, 83]. The associated conditions include autoimmune thyroid disease, pernicious anemia, Addison's disease, lupus erythematosus, rheumatoid arthritis, and adult-onset autoimmune diabetes mellitus [84, 85]. Based on these associations, it is reasonable to screen for selected diseases (thyroid-stimulating hormone, thyroid antibodies, fasting blood glucose level), mainly in children and young women [86, 87]. Investigation of additional antibodies should be performed only if the patient's history, family history, or physical examination suggests other autoimmune diseases [88].

Complementary Examinations

The Wood's lamp, a device that emits UVA waves, is useful for highlighting areas of pigment loss on patients with fair skin [89]. Rarely, a skin biopsy is necessary for the diagnosis: if the diagnosis is uncertain, histopathologic evaluation may be helpful to differentiate vitiligo from other disorders [90]. Punch biopsies from lesional and perilesional skin are recommended. Biopsy findings are typically unremarkable with only sparse cellular infiltrates and few or no melanocytes [91]. Melanocytes on the pigmented edge of vitiliginous skin are larger, often vacuolated, and with long dendritic processes filled with melanin granules. Active lesions may have a lichenoid interface dermatitis [89].

Diagnosis

Box. 23.1 Vitiligo: Diagnosis
Depigmented patches of skin (full-body skin examination should be performed to detect possible hidden lesions)
Wood's lamp (useful and practical, inexpensive)
Histopathology (rarely necessary)

Differential Diagnosis

The differential diagnosis of vitiligo is broad. However, an adequate history and a careful physical examination generally yield a straightforward diagnosis. The differential diagnosis includes postinflammatory hypopigmentation, chemically induced depigmentation, tinea versicolor, pityriasis alba, idiopathic guttate hypomelanosis, nevus depigmentosus (achromic nevus), hypomelanosis of Ito, piebaldism, morphea, and leprosy, among others. Rarely, patients with cutaneous melanoma may present with hypopigmented patches resembling vitiligo [92]. In these patients, vitiligo-like depigmentation is thought to be a marker of an immune response against melanoma cells and may be an indicator of favorable prognosis in advanced disease [93].

Therapeutic Approach

Although vitiligo is still considered by many physicians a cosmetic disorder, its effects can be psychologically devastating, having a significant impact on quality of life. Several treatment modalities are available, although none of them produces predictably good results in all patients. Treatment options include topical corticosteroids, calcineurin inhibitors, vitamin D derivatives, phototherapy, surgical techniques, oral steroids, and systemic immunosuppressants for selected refractory cases. Combinations of treatments have also been tested in the past few years. In addition to repigmentation therapies, the use of sunscreens minimizes tanning, therefore reducing

the contrast between affected and normal skin. Makeups are helpful to camouflage depigmented areas in lighter-skinned patients.

The treatment goals are stabilization of the depigmentation process and repigmentation. Therapy should begin early in the course of the disease for better responses. The choice of therapy depends on the extent, location, and activity of disease as well as the age, skin phototype, and motivation to undergo treatment. At least 2–3 months are usually required to determine whether a specific treatment is effective. Some areas of the body such as the face, neck, mid-extremities, and trunk are more likely to have a better response to therapy. Conversely, distal extremities and lips are the most resistant to treatment. Repigmentation typically occurs in a peripheral and/or perifollicular pattern.

Topical Corticosteroids

Topical corticosteroids are considered a first-line and an adjunctive therapy for vitiligo, owing to its low cost and ease of application. However, its use is limited because of the risk of side effects including epidermal atrophy, telangiectasia, striae, steroid folliculitis, and side effects associated with systemic absorption [94]. Therefore, high-potency topical corticosteroids are more appropriate for small areas, being more effective on the face, elbows, and knees, although some authors prefer to use low-power corticosteroids on the face and flexural areas [95]. A meta-analysis demonstrated higher efficacy and safety of class 3 topical corticosteroids compared with class 4 and intralesional corticosteroids in the treatment of localized vitiligo [96]. To reduce the likelihood of local side effects, its use may be sparse or alternated with other topical therapies. In localized vitiligo, high-power topical corticosteroids should be used for 2 months, and low-power corticosteroids or other immunomodulators should be considered to decrease the risk of adverse events [97]. If no clinical response is seen with topical corticosteroids within 3–4 months, their application should be suspended [98].

The efficacy of topical corticosteroids to treat vitiligo has been supported by many studies. In a retrospective study of 101 children treated with high- or moderate-potency corticosteroids, both groups showed repigmentation in 64% of cases, stabilization in 24%, and worsening in 11%. In the stratified analysis according to corticosteroid potency, no difference was found between the moderate- and high-power drugs ($p = 0.03$), nor in the incidence of local adverse events ($p = 0.3$), However, this study should be interpreted with caution because of its variable product dosages, as well as the small number of cases in the group applying moderate-power corticosteroids [94]. Complete repigmentation rates have been reported to be as high as 49.3% [99]. It is important to mention that higher response rates are seen in children than in adults; and head and neck lesions tend to have the greatest response to treatment [100].

In summary, topical corticosteroids are generally considered a safe first-line treatment option. Head and neck lesions tend to have a better response. Local side effects limit long-term use and merit frequent monitoring. Treatment combination not only reduces the possibility of side effects but also increases response rates [101].

Calcineurin Inhibitors

Calcineurin inhibitors are valuable in treating vitiligo because they have immunomodulatory effects without the typical adverse events of corticosteroids. Calcineurin is an intracellular protein in lymphocytes and dendritic cells. When activated, it acts as a transcription factor for cytokines, such as IL-2 and tumor necrosis factor α (TNF-α). Compared with healthy controls, patients with vitiligo have elevated IL-10, TNF-α, and interferon-γ. Treatment with tacrolimus decreases tissue counts of TNF-α and increases melanocyte and melanoblast proliferation [102].

There are two available topical calcineurin inhibitors: pimecrolimus and tacrolimus. Both may be an effective therapy for vitiligo; however, most of the evidence of their use comes from small case series and uncontrolled trials

[103–105]. Response rates after 3–6 months range from 63% to 89% [103, 105–108] with the head and neck showing the best results. Mean repigmentation rates range from 26% to 72.5% [109, 110]. Lesions on the arms and legs that were previously nonresponsive to topical therapy may improve with occlusion during the night [107, 111]. Calcineurin inhibitors produce results slightly inferior to equivalent repigmentation rates when compared with corticosteroids, although the effect occurs earlier in the course of treatment [99, 112].

In adults with generalized symmetric types of vitiligo, in a small study, topical pimecrolimus for 8 weeks induced 50–100% repigmentation (a similar degree to that seen with topical clobetasol) for lesions on the trunk or extremities. Stinging was a side effect [113]. In children with generalized symmetric vitiligo, topical tacrolimus used over an 8-week period induced nearly 50% repigmentation of vitiligo lesions (a similar degree to that seen with topical clobetasol) for lesions on the face or thorax but not the hands. Stinging was a side effect [99]. Topical calcineurin inhibitors may also be used as adjunctive therapy. The combination of topical tacrolimus with excimer UV radiation appeared to enhance the degree of repigmentation over that for excimer alone, for UV-sensitive sites but not for areas over bony prominences [114, 115].

Regarding safety, both are safe for short-term or intermittent long-term use. Common side effects include erythema, pruritus, burning, and irritation [99, 104–106]. In 2005, the Unites States Food and Drug Administration (FDA) issued an alert about a possible link between topical tacrolimus and pimecrolimus and cases of lymphoma and skin cancer in children and adults, and in 2006 placed a "black box" warning on the prescribing information for these medications [116]. This link is very controversial since it was based on the theoretical risk arising from the systemic use of calcineurin inhibitors in transplant recipients and animal studies. Extensive safety data have been analyzed from more than 20,000 clinical trial participants using tacrolimus ointment. To date, there is no evidence to suggest that there is an increased risk of lymphoma or nonmelanoma skin cancer in adults or children using tacrolimus ointment [117].

In summary, the off-label use of topical calcineurin inhibitors has been shown to be safe and effective in the treatment of vitiligo in both adults and children. Given their lack of local side effects and efficacy comparable with that of topical corticosteroids, they are appropriate for intermittent long-term use. Face and neck lesions respond best, and occlusion may help with recalcitrant lesions on the extremities. Recent data suggest that combination with phototherapy increases responses.

Topical Vitamin D Analogs

Topical vitamin D3 analogs (calcipotriol and tacalcitol) have been reported as a treatment option for vitiligo, either alone or combined with other modalities. Most studies evaluated calcipotriol as adjuvant therapy, but some small studies of calcipotriol monotherapy in children have shown high response rates. Calcipotriol has lower response and repigmentation rates when compared with topical corticosteroids [118]. However, combining both has shown increased repigmentation rates and reduced onset of repigmentation. Areas that respond to treatment tend to have a greater stability of repigmentation compared with either as monotherapy [118, 119]. Furthermore, combination therapy is effective in some previously corticosteroid nonresponsive patients [119].

The use of calcipotriol combined with phototherapy has yet to be elucidated. Some studies suggest that there is no benefit of combining calcipotriol and narrow-band UVB phototherapy, and that it may actually delay repigmentation [120–122]. Other studies, however, report a decreased number of exposures and lower cumulative irradiation dosage required for repigmentation when added to narrow-band UVB and PUVA phototherapies [123, 124].

In summary, topical vitamin D3 analogs are safe and provide the most benefit especially when combined with topical corticosteroids. More studies are necessary to address their real

benefit as monotherapy. Combination therapy with phototherapy is controversial and requires further research.

Systemic Corticosteroid Therapy

Systemic corticosteroid therapy may be used in cases of extensive vitiligo with rapid progression. The use of mini-pulses has been tried in order to minimize adverse events inherent to daily treatment. A meta-analysis demonstrated a lower incidence rate of systemic and cutaneous adverse events with the mini-pulse regimen when compared with daily use of corticosteroids [96].

Some of the adverse events of systemic corticosteroids include insomnia, acne, agitation, menstrual disturbances, weight gain, hypertrichosis, and adrenal insufficiency. In one study of vitiligo patients treated with intravenous steroids, 69% reported systemic side effects [19]. Although systemic corticosteroids have potential in treating specific patients with vitiligo, the lack of data on efficacy and optimal dosing parameters warrant further research.

Systemic Immunosuppressants

Immunosuppression has a clear role in treating vitiligo. However, aside from corticosteroids, there is almost no literature regarding the use of systemic immunosuppressants. This is probably related to the high-risk side-effect profile.

In one randomized controlled study, daily low-dose azathioprine increased the benefits of PUVA phototherapy in vitiligo, without serious side effects [125]. In a recent study that compared oral corticosteroid mini-pulse and low-dose methotrexate in the treatment of unstable vitiligo, both agents were equally effective in controlling the disease activity of vitiligo [126]. The authors suggested that methotrexate can be used in patients with active vitiligo whenever corticosteroids are contraindicated. Another study, however, showed no benefit of methotrexate after 6 months of treatment in six patients who had had vitiligo for several years [127, 128].

Phototherapy and Photochemotherapy

Narrow-Band UVB

This phototherapy modality involves the emission of a wavelength spectrum from 310 to 315 nm, with a peak emission at 311 nm. As no photosensitizer is used, ocular or gastrointestinal side effects are nonexistent [129]. In addition, narrow-band UVB can also be used in children, pregnant or lactating women, and individuals with hepatic or kidney dysfunction [130].

Its mechanism of action has not been completely understood. The induction of T-lymphocyte apoptosis by narrow-band UVB in association with melanocyte mitogenesis, melanogenesis, and migration from outer root sheaths of hair follicles seem to play a role in repigmentation of vitiligo lesions (Fig. 23.2) [129].

Regarding narrow-band UVB therapeutic response, in a large open trial [131] with 110 patients (97 non-segmental and 13 segmental) treated twice weekly for a mean of 7.8 months, 48% of the nonsegmental group showed a good response (>75% repigmentation), 27% a moderate response (25–75% repigmentation), and 25% mild response (<25% repigmentation). When analyzed by site, the patients showed marked response in 76.3% in face lesions, 41.9% in trunk lesions, and 37.6% in limb lesions. None of the patients achieved marked response in the acral areas. In segmental vitiligo, narrow-band UVB phototherapy was less effective. Early treatment onset appears to be correlated with better therapeutic outcomes in segmental vitiligo [132].

As the majority of comparison studies have shown that it is more effective than other phototherapeutic modalities, narrow-band UVB is considered the first-line treatment for generalized vitiligo [129, 133, 134].

The long-term risks of narrow-band UVB in vitiligo patients remain unclear. Although no data are available regarding carcinogenesis in patients with vitiligo, individuals with diseases other than vitiligo receiving narrow-band UVB treatment had an increased risk for basal cell carcinoma in some studies [135, 136].

308-nm Excimer Laser

This equipment emits a monochromatic, coherent, and collimated laser light of 308 nm, inducing photobiological effects similar to those of narrow-band UVB. As a laser, it has the ability to deliver high fluences in a short time. It also has the advantage of being able to treat targeted areas, sparing healthy skin [129]. Repigmentation greater than 75% is usually reported in 12.5–61% of treated lesions according to several studies [137–142]. In an intrapatient comparison of 308-nm narrow-band UVB versus 308-nm Excimer laser on eight patients with symmetric lesions, a slightly higher repigmentation in the Excimer-treated area was observed [143]. Combined treatment with topical tacrolimus has been shown to be useful for accelerating initial repigmentation at the first 6 months of therapy [144]. The disadvantages of this method are the limited size of spots, which can be impractical for treating large areas (>20% of total surface body area), besides the high costs of purchase and maintenance of the equipment [129].

Excimer Lamp

The specific 308-nm radiation wavelength is also available in an incoherent form, commonly called the excimer lamp. Several trials have utilized the lamp for the treatment of vitiligo, reporting excellent repigmentation (>75%) for 25–50% of patients [145–149].

A comparison study of excimer laser versus excimer lamp showed that both devices had similar efficacy [141], although the excimer lamp takes more time to deliver the required dose, making the procedure time consuming for patients with large areas to be treated.

Psoralen plus Ultraviolet A (PUVA)

> **Box 23.2 PUVA**
> PUVA therapy was first used in ancient Egypt and in India, more than 3,000 years ago, when extracts from the plants *Psoralea corylifolia*, in India, and *Ammi majus*, in Egypt, were used as a topical and oral treatments for vitiligo.

Photochemotherapy or PUVA therapy was the mainstay for vitiligo management for a long period, but nowadays is a second-line treatment for adults. It consists in body irradiation with UVA (320–400 nm) after the patient takes or applies a photosensitizer drug. The most used oral photosensitizer is 8-methoxypsoralen (8-MOP), which is taken 2 h before irradiation, at a mean dose of 0.6 mg/kg [129].

Topical PUVA is a good alternative for localized vitiligo in adults and children over 2 years. However, care must be taken with topical preparations of psoralens, as even lower concentrations (usually 0.1% and below) of 8-methoxypsoralen can produce severe phototoxicity. Perilesional hyperpigmentation can be encountered in most cases [129].

Sunlight can also be used as a source of UVA, a therapy called PUVA sol. It is commonly used in countries where the facilities for artificial sources of light are often lacking and where sunlight is in abundance. Although PUVA sol is an inexpensive modality, it lacks adequate controlled parameters, making it unreliable and more prone to phototoxic adverse effects [129, 150].

Commonly encountered short-term side effects include cutaneous phototoxicity, nausea, insomnia, headache, and lightheadedness. Significant long-term effects such as photoaging and increased risk of skin carcinogenesis (melanoma, squamous cell carcinoma, and basal cell carcinoma) are also noteworthy, especially in patients with higher cumulative doses [129].

Contraindications for PUVA are history of skin cancer, premalignant skin lesions, cataracts, altered liver function, pregnancy, lactation, and concomitant immunosuppressive or phototoxic treatment [129]. The lower response rate and greater side effects of PUVA in comparison with narrow-band UVB has led to the first being replaced increasingly by the latter [129, 133, 134].

Surgical Management

Autologous melanocyte transplantation is another treatment option for selected patients with stable disease that has failed to respond to previous clinical treatments [151]. It can produce good

results even for traditionally refractory sites such as distal extremities, elbows, knees, nipples, eyelids, and lips [152].

Although all types of vitiligo are suitable for melanocyte transplantation, segmental vitiligo tends to have a better outcome [153]. Therefore, correct classification of the disease is crucial, as it influences patient prognosis. Disease stability is the most important factor for a successful surgical outcome [154]. Although there is no absolute consensus about stability period criteria, most authors define it as the absence of new lesions and no extension of pre-existing ones over the past year [151, 154, 155]. In doubtful cases, a test can be done implanting 4–5 mini-grafts with a 1- or 1.2-mm punch within the area to be treated and evaluating the repigmentation halo around such grafts after 3–4 months [156]. The absence of Koebner phenomenon in surgical candidates is also important, since surgical manipulation of donor and recipient areas may induce new achromic lesions [151]. Surgical modalities are classified as tissue or cellular techniques according to the type of transplanted graft [151, 155]. Most techniques require de-epithelialization of the recipient site in order to receive the tissue or cellular graft. Generally this is done with dermabrasion, a widely used and cost-effective procedure. Pre- and postprocedure phototherapy is recommended as it is related to better results [157].

Tissue Techniques

Punch Grafting

Punch grafting is a simple, low-cost, and widely used technique for surgical treatment of vitiligo. It consists in harvesting multiple small punches (1–3 mm) from the donor site (e.g., retroauricular area, buttocks, thighs) and transplanting them to the recipient area, which is prepared with a similarly sized or slightly smaller punch [158, 159]. Larger grafts often produce a cosmetically undesirable effect known as cobblestone appearance, which can resolve spontaneously or with treatments such as electrofulguration [160]. Punch grafting is typically limited to the treatment of small areas, but the use of motorized punch equipment can substantially reduce the procedure time, allowing treatment of larger sites [161].

This technique is successful in most patients with vitiligo. In a large study including 880 patients, 90–100% repigmentation was achieved, in 74.55% of them within 2 years of follow-up [158].

Suction Blister Epidermal Graft (SBEG)

This procedure involves induction of suction blisters on the donor area (usually thighs or arms) by applying prolonged vacuum with the aid of a syringe or specific equipment for this purpose (Fig. 23.5a) [151]. It has some advantages over
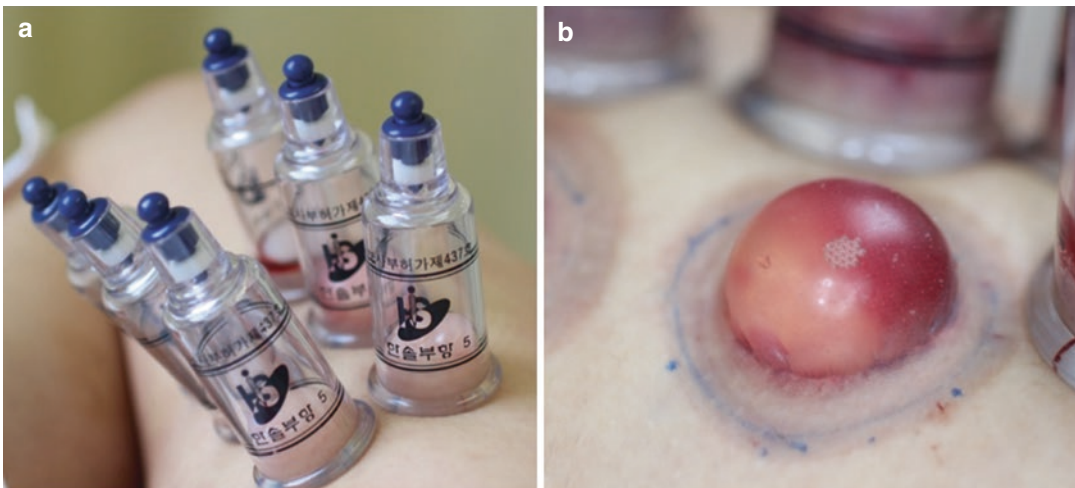
Fig. 23.5 (**a**) Suction apparatus positioned on the inner thigh. (**b**) Blister formed after 50 min of suction

Fig. 23.6 (**a**, **b**) Preoperative register of segmental vitiligo in the forehead and left cheek. (**c**, **d**) 11 weeks postoperatively, with 85% diffuse repigmentation and good color match

the punch graft method, as the donor area heals with minimal scarring and postinflammatory pigmentation [162]. Furthermore, being a purely epidermal graft there is no cobblestone effect.

According to a recent study, the SBEG technique produces good to excellent results (65–100% repigmentation) in 80% of patients (Fig. 23.6). Although cost-effective, this method is considered a time-consuming technique since it takes approximately 2 h to form a blister using

a 10-ml syringe (Fig. 23.4b). This time can be shortened through infiltration of the dermis with anesthetics or by using a heat lamp over the donor area [163].

Split-Thickness Skin Grafting

Split-thickness skin grafts have the advantage of treating large areas effectively (90–100% repigmentation) with a single procedure. The graft is obtained with the aid of a dermatome, a

procedure that requires skill and experience [164]. Furthermore, the incompatibility of colors in the recipient area and scarring in the donor area are potential side effects of this technique [155].

Cellular Techniques

Noncultured Epidermal Cell Suspension (NCES)

In this technique a thin split-thickness skin graft is taken from the donor area with the help of a shaving blade or a dermatome (Fig. 23.7). After this procedure, the skin sample is incubated at 37 °C in a trypsin–ethylenediamine tetraacetic acid (EDTA) solution, which separates the epidermis from dermis. After some additional steps, a melanocyte–keratinocyte cell suspension is obtained and transferred to the denuded recipient area (Fig. 23.8). This method has the advantage of a donor-to-recipient expansion ratio ranging from five- to tenfold, being able to treat large areas with good results [151, 155]. Good to excellent repigmentation (75–100%) can be achieved in 89% of patients [165]. As disadvantages, this technique requires skill and experience to take the split-skin graft and some specialized laboratory equipment [151].

Noncultured Extracted Hair Follicle Outer Root Sheath Cell Suspension (NCORSHFS)

In this procedure, a cell suspension is obtained from hair follicles harvested using a follicular unit extraction (FUE) technique with the help of a small punch (Fig. 23.9a). Depending on the area to be transplanted, approximately 15–25 pigmented follicles are extracted per subject. Once extracted, the follicular units undergo a laboratory process similar to the NCES procedure to obtain a cell suspension (Fig. 23.9b) [166]. Obtaining cells from hair follicle has some advantages. The hair follicle is an important reservoir of melanocytes and their precursor cells. Furthermore, scarring in the donor area is unnoticeable with the FUE method [167]. In a randomized comparative study of NCES versus NCORSHFS with 30 patients, good to excellent (75–100%) repigmentation extent was achieved in 92% and 78% of lesions, respectively, although this difference was not statistically significant [168].

Cultured Cell Suspension

In vitro cultivation of melanocytes with or without keratinocytes can dramatically increase the transplanted cell number (Fig. 23.10). Therefore, cells from a small piece of normal
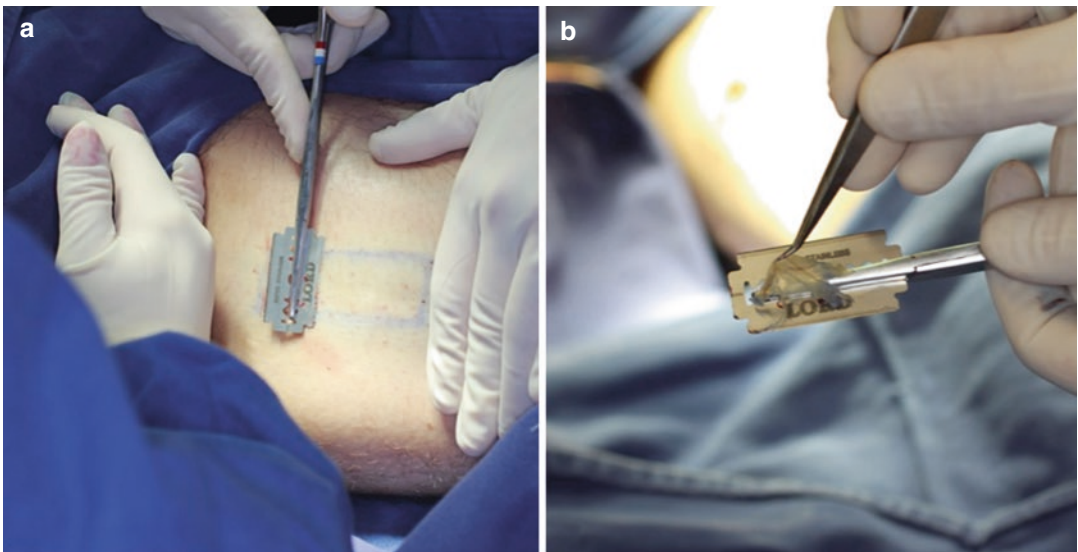
Fig. 23.7 (**a**) A thin split-thickness skin grafted being harvested in the inner thigh with the help of a shaving blade. (**b**) Split-thickness graft obtained. Note the ultrathin semi-transparent appearance
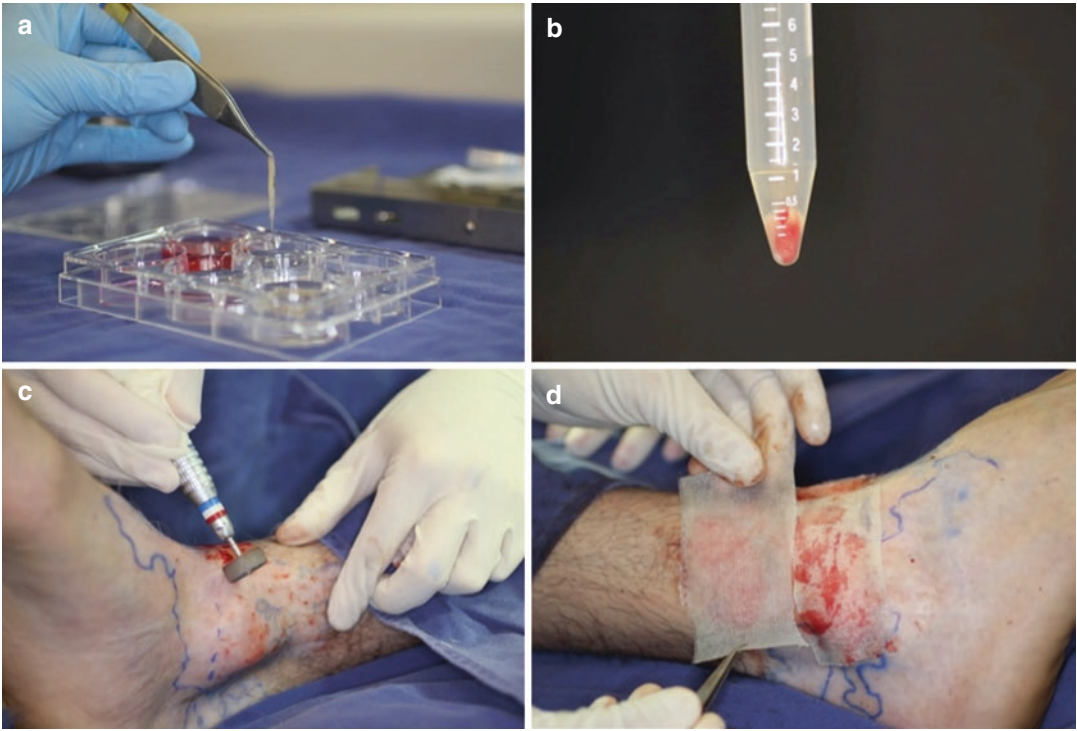
Fig. 23.8 (**a**) Skin sample 50 min after 37 °C incubation in trypsin–EDTA solution. In this phase, the dermis is detached from the epidermis and epidermal cells are released in the suspension. (**b**) Suspension after centrifugation. Note the cell pellet in the bottom of the tube. (**c**) Recipient area being dermabraded in order to receive cell suspension. (**d**) After receiving the cells, the recipient area is covered with a wound dressing for 7–10 days
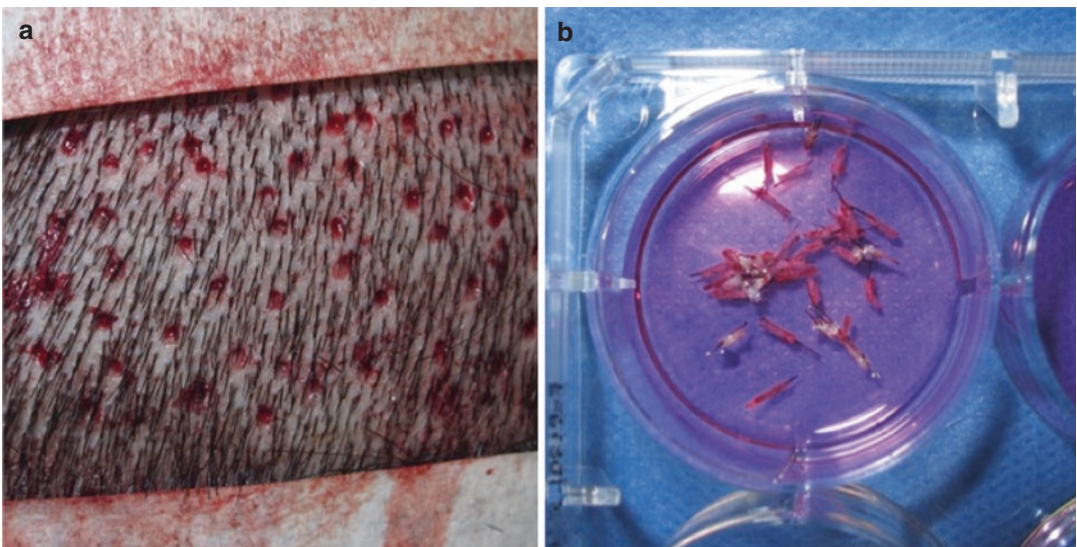
Fig. 23.9 (**a**) Occipital donor area after FUE procedure. (**b**) Follicular units in trypsin–EDTA solution
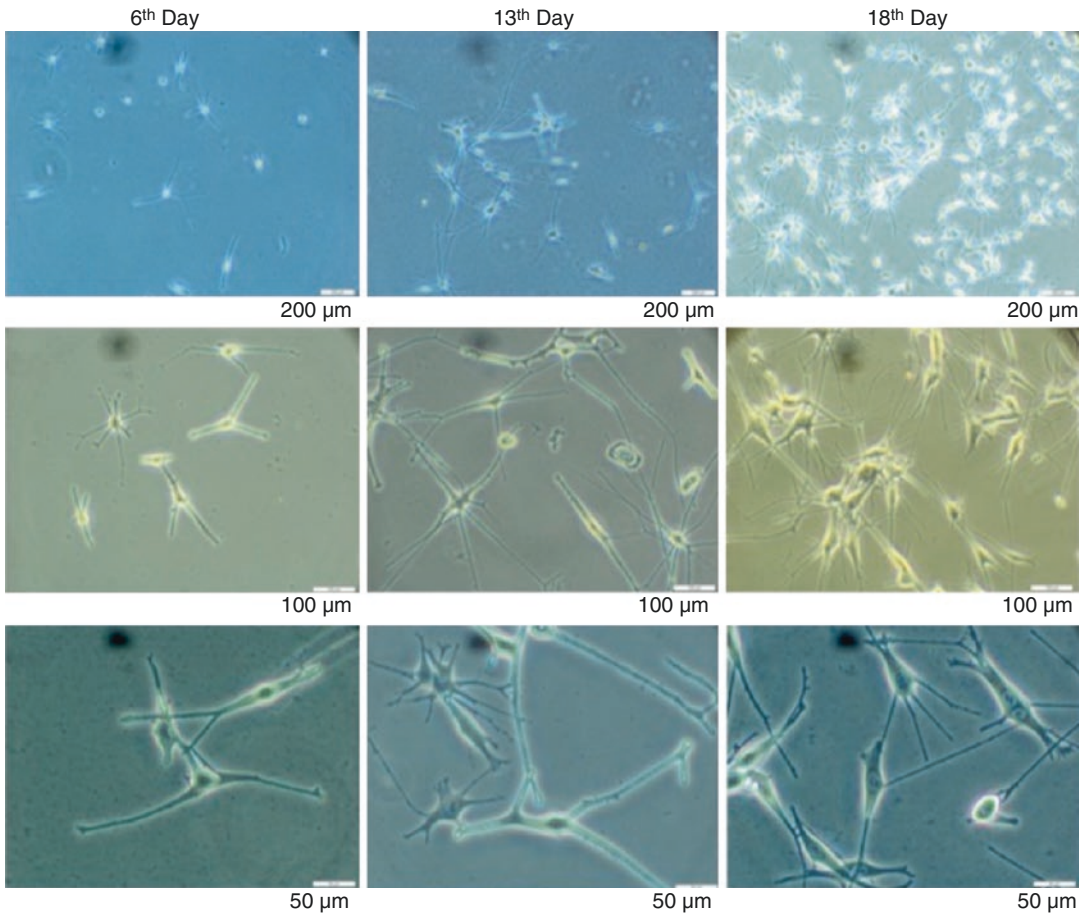
Fig. 23.10 Optical micrograph of a human primary melanocyte culture isolated from skin explants (40×, 100×, and 200× magnification, from top to bottom). The cells were pretreated with geneticin to eliminate fibroblasts and keratinocytes. Throughout 18 days after treatment with geneticin, melanocytes were cultured in a medium supplemented with growth factors (basic fibroblast growth factor and hepatocyte growth factor), allowing the maintenance and proliferation of cells (Image courtesy of Dr. Renata Helena Monteiro Sindeaux and Mariana Kraft Soares, Advanced Core of Molecular Research, Pontifical Catholic University of Parana, Brazil)

skin can be used to treat large depigmented areas, this being one of the major advantages of this technique [169]. Furthermore, this method can provide even greater repigmentation rates relative to the noncultured techniques [169, 170]. The cost factor, the need of cell culture expertise, and requirement of specific laboratory materials are disadvantages [151]. Furthermore, as the growth medium used in cultures contains various types of mitogenic factors, long-term follow-up is recommended because of the theoretical potential of the human melanocytes to transform at a later date after transplantation [170].

Glossary

1. *Single nucleotide polymorphism (SNP)*: A variation in a single nucleotide at defined positions within genomes and are responsible for individual phenotypic characteristics, including a person's propensity toward complex disorders. Each variation is present to some appreciable degree within a population.
2. *Regulatory T Cells* (*TREGs*): A subpopulation of T cells that modulate the immune system and are defined based on expression of CD4, CD25, and the transcription factor FoxP3.

TREGs are crucial mediators of self-tolerance in the periphery, preventing autoimmune diseases and limiting chronic inflammatory diseases.

3. *Koebner phenomenon*: or isomorphic response; refers to the appearance of lesions along a site of injury.

4. *Mosaicism*: A condition whereby cells within the same person have a different genetic makeup, i.e., different cells in the same individual have different numbers or arrangements of chromosomes. It is called "mosaicism" because, in a way, the cells of the body are similar to the tiles of a mosaic. This condition can affect any type of cell, including: blood cells, sperm cells, and skin cells.

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Autoimmune Bullous Dermatoses

Hiram de Almeida Larangeira Jr.

Key Points summary
- Bullous dermatoses are acquired conditions arising from pathogenic autoantibodies against structural proteins of cell–cell and cell–matrix adhesions in the skin and mucous membranes
- The clinical presentation of bullous dermatoses shows skin and mucosal fragility with blisters, vesicles, and/or erosions
- Treatment of bullous dermatoses should suppress antibody production with immunosuppression.

Introduction

Autoimmune bullous dermatoses are acquired diseases associated with pathogenic autoantibodies against structural proteins that maintain cell–cell and cell–matrix adhesions in the skin and mucous membranes. The clinical presentation is characterized by fragile skin and/or mucous membranes with blisters, vesicles, and/or erosions.

These dermatoses have been classified as acantholytic (or intraepidermal) bullous dermatoses – the pemphigus group (caused by desmosomal damage) – and nonacantholytic (or subepidermal), caused by hemidesmosomal damage, belonging to the bullous pemphigoid group. In dermatitis herpetiformis, a condition with subepidermal blisters, epidermal detachment is secondary to an inflammatory reaction.

Epidemiology

The bullous diseases particularly affect those in middle age (onset typically at 40–60 years of age) [1, 2]. In Germany an estimated 2,000 new cases of autoimmune blistering skin diseases occur per year. Pemphigus vulgaris is the most common type [3]. Pemphigus foliaceus, triggered by an environmental agent, is endemic in certain regions of central Brazil [4].

Bullous pemphigoid affects elderly individuals, with an annual incidence estimated to range from 12 to 60 new cases per million people [5]. Dermatitis herpetiformis (DH) is a rare bullous dermatosis whose prevalence varies according to the study population [6, 7].

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Etiopathogenesis

Skin epithelial cells, keratinocytes, have two major features, namely the synthesis of keratin, which culminates in the formation of the protective barrier (stratum corneum), and adhesion - intercellular and to the dermis, which gives the epithelium its mechanical strength.

Intercellular adhesion is provided by desmosomes. A desmosome consists of proteinaceous plaques attached to the cytosolic face of the plasma membranes of adjacent cells connected by transmembrane linker proteins. They interact, forming a network that binds two cells together.

The most important proteins in intercellular adhesion are desmogleins 1 (DSG1) and 3 (DSG3). DSG1 is expressed throughout the skin and DSG3 in the mucous membranes. When DSG3 is damaged, usually by immunoglobulin G (IgG), adhesion loss occurs in the mucous membrane. This results in loss of adherence of epithelial cells and the formation of intraepithelial blisters, referred to as mucosal pemphigus vulgaris. When the pathogenic IgG damages the DSG1, the skin becomes fragile and blisters form, referred to as pemphigus foliaceus. Some individuals may damage both DSGs, affecting skin and mucous membranes, referred to as mucocutaneous pemphigus vulgaris, the most severe type of pemphigus. Damaged desmosomes result in keratinocyte detachment (acantholysis) (Fig. 24.1a). In these cases the hemidesmosomes are normal and the basal keratinocytes remain adhered to the basal membrane (Fig. 24.1a), revealing a suprabasal cleavage, typical of pemphigus vulgaris.

The epidermis is adhered to the dermis by a structure that is similar that of the desmosomes, known as hemidesmosome, which attaches basal keratinocytes to the extracellular matrix. Transmembranous proteins connect the hemidesmosomal plaque of an epithelial cell to the underlying basement membrane. Similar to pemphigus, pathogenic IgGs damage these proteins, causing
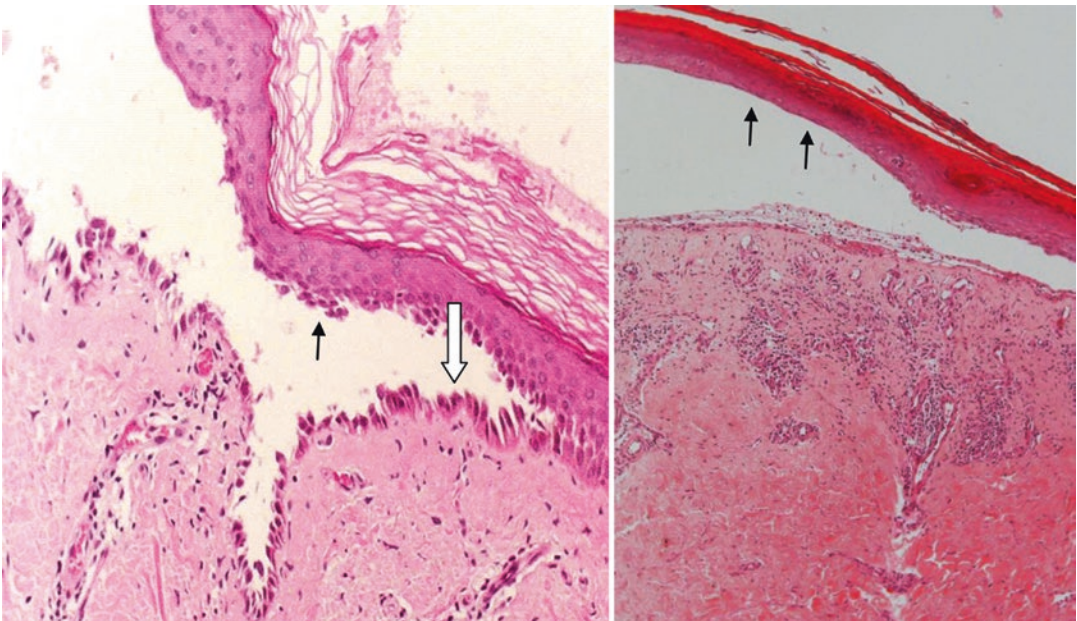
Fig. 24.1 (**a**) Typical histologic features of a bullous dermatosis caused by desmosomal damage with acantholytic keratinocytes (due to adhesion loss) (*thin arrow*). Note that the basal keratinocytes remain attached to the basal membrane (*thick arrow*), since the hemidesmosomes are normal, revealing a suprabasal cleavage. (**b**) Typical histologic features of a bullous dermatosis caused by hemidesmosomal damage, without acantholysis. Note that there are no loose cells in the epidermis (*arrows*) and there is complete detachment of the epidermis, known as dermoepidermal cleavage (Photos courtesy of Prof. Mirian Sotto, University of São Paulo)

complete loss of epidermis (Fig. 24.1b), although without acantholysis, since the desmosomes (formed by other proteins) remain intact. This disease is called bullous pemphigoid.

Dermatitis herpetiformis does not fall into this category because the pathogenic immunoglobulin deposits cause no direct damage to either desmosomal or hemidesmosomal proteins. A deposit of IgA occurs in the upper dermis (papillary dermis). Neutrophils are then attracted to this region, and probably an inflammatory response is triggered, causing blisters and vesicles. Gluten-sensitive enteropathy may be an associated condition; therefore, diet and follow-up by a gastroenterologist are recommended.

Clinical Presentation

Mucosal pemphigus vulgaris is a very frequent clinical presentation [2]. Patients complain of lesions that affect mainly the oral mucosa, with erosions (Fig. 24.2). Sometimes there is detachment of part of the epidermis with elimination of a tissue lamina. It may also affect the conjunctiva, nose, pharynx, esophagus, genitals, and anus [8], causing major impact on the patient's quality of life. After onset in the mucous membranes, some patients develop a disseminated form of the disease, mucocutaneous pemphigus vulgaris, which can also be the initial clinical presentation of the disease. In such cases, disseminated blisters and erosions also occur (Fig. 24.3).

Pemphigus foliaceus is confined to the skin and there is no involvement of mucous membranes. As the intraepidermal cleavage is a little higher than in pemphigus vulgaris, the blisters are flaccid and sometimes absent, and rupture very easily, while only erosions may be seen. The lesions are often scaly and crusty (Fig. 24.4), closely resembling the appearance of seborrheic dermatitis [9].

Fig. 24.2 Erosions on the back of the tongue and in the oropharynx, characterizing mucosal pemphigus vulgaris

Fig. 24.3 Blisters and erosions disseminated in mucocutaneous pemphigus vulgaris (Photo courtesy of Dr. Cláudia Santi, Hospital das Clínicas, University of São Paulo)
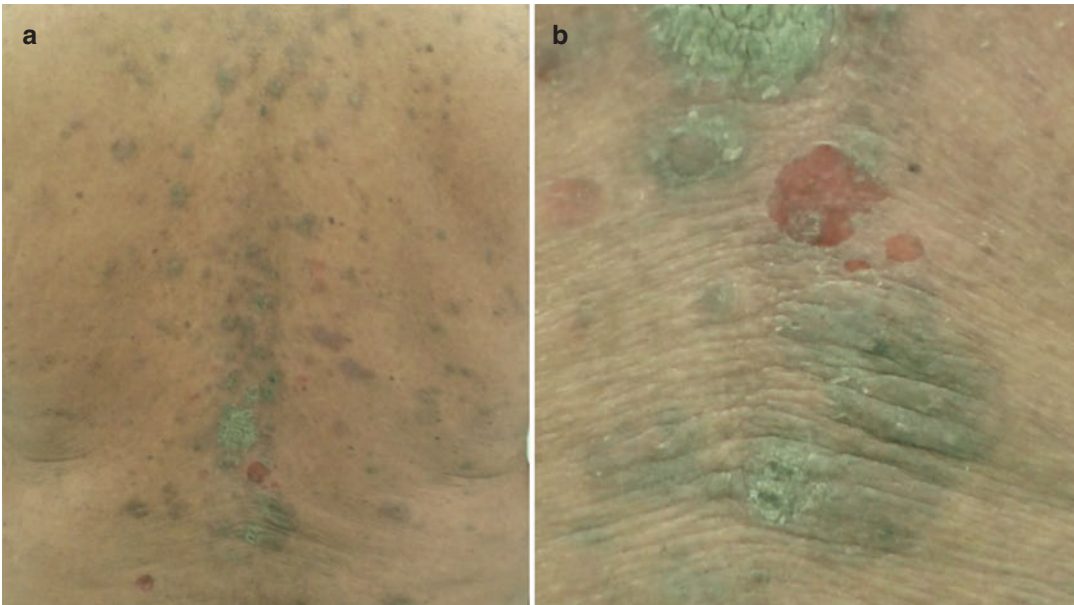
Fig. 24.4 (**a**) Disseminated crusted lesions and some erosions in pemphigus foliaceus. (**b**) Detail of the lesions

Fig. 24.5 Disseminated blisters in bullous pemphigoid. There are more inflammatory changes than in pemphigus vulgaris (Fig. 24.3), since the lesions may be preceded by urticarial plaques (Courtesy of the Dermatology Department, Santa Casa de Porto Alegre).

Fig. 24.6 Grouped vesicles in dermatitis herpetiformis (Courtesy of the Dermatology Department, Santa Casa de Porto Alegre).

Diagnosis

Bullous pemphigoid is characterized by tense blisters (Fig. 24.5) on the skin, which may be preceded by pruritic urticaria [5]. Mucosal involvement is rare.

Dermatitis herpetiformis (DH) is clinically characterized by grouped vesicles (Fig. 24.6), such as in herpes simplex. Many patients present discrete lesions without the formation of vesicles, only grouped crusts. In mild cases, the frequently affected locations (elbows, knees, and buttocks) may be useful for a differential diagnosis.

Conventional light microscopy can establish the diagnosis, showing partial loss of the epidermis with acantholysis in patients with pemphigus and total loss of the epidermis without acantholysis in the bullous pemphigoid group (Fig. 24.1).

Direct immunofluorescence complements the diagnosis, showing the deposit of IgG in the epithelium with intercellular pattern, typical of pemphigus (where desmosomes are located) (Fig. 24.7a) and a linear pattern along the basement membrane zone, typical of the bullous
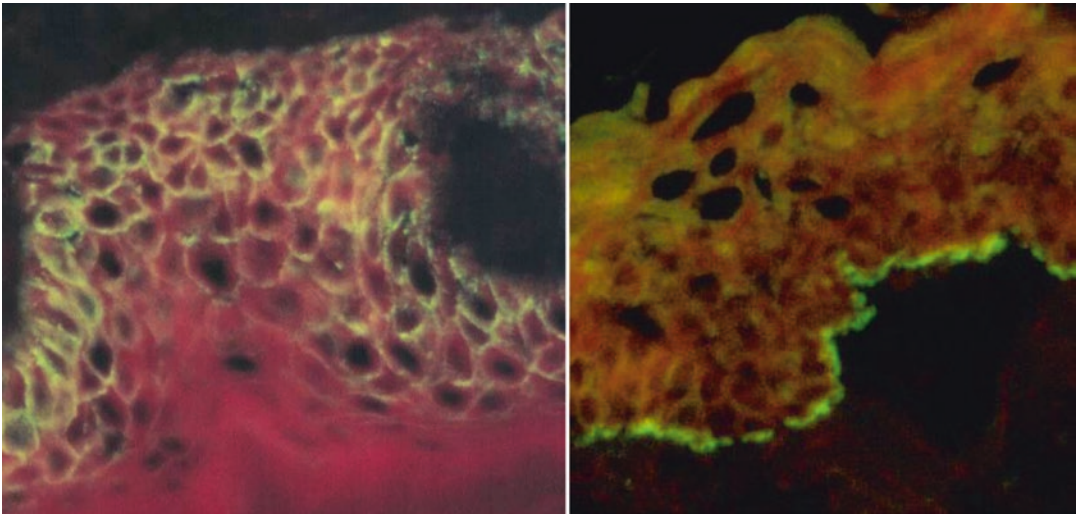
Fig. 24.7 Typical findings of direct immunofluorescence. (**a**) Intercellular pattern (*greenish staining*), demonstrating that the pathogenic antibodies move toward desmosomal transmembranous proteins. (**b**) Linear pattern along the basal membrane zone (*greenish line*), demonstrating that the antibodies move toward the proteins in this zone; in the case of bullous pemphigoid, toward the hemidesmosomal proteins (Photos courtesy of Dr. Cláudia Santi, Hospital das Clínicas, University of São Paulo)

pemphigoid group (Fig. 24.7b). Biopsy is necessary to perform this examination, and the tissue should not be fixed in formalin but placed into transport medium for fresh examination. Indirect immunofluorescence, performed with patient's serum, avoids the biopsy and can detect ciculating autoantibodies at a lower cost.

Commercial enzyme-linked immunoassay (ELISA) tests for DSG1 and DSG3 autoantibodies detected in the sera of patients are now available, but at higher cost. For dermatitis herpetiformis, optical microscopy frequently provides atypical results, as vesicles are clinically rare. Direct immunofluorescence reveals IgA deposits in the upper dermis. Similarly for the diagnosis of pemphigus, ELISA can be used for detection of IgG against the proteins involved (endomysium and tissue transglutaminase antibodies), and can be helpful in the diagnosis.

Therapeutic Approach

The first-line treatment of pemphigus and pemphigoid is high-dose oral corticosteroids. One can start with 1 mg/kg/day of prednisone and decrease the dose, according to clinical response [10].

If patients do not respond to corticosteroids, another immunosuppressant (azathioprine or methotrexate) can be used. Methotrexate can be taken at 15 mg per week [11], as in other autoimmune diseases, e.g., psoriasis and rheumatoid arthritis. The weekly dosing schedule is well tolerated and convenient, but its use should be carefully explained to patients, since accidental doses have been reported when patients took this dose daily instead of weekly. Potential adverse effects from this drug require monitoring of hematologic, renal, and hepatic function; alcohol abstinence and exclusion of viral hepatitis are mandatory.

Some authors recommend initial administration of immunosuppressant with concomitant oral corticosteroid to lessen the cumulative dose of corticosteroid.

Mild cases of bullous pemphigoid can be treated with topical corticosteroids, as it usually affects the elderly and the effects of prolonged use of oral corticosteroid can be avoided. A good response has been reported with oral tetracycline, which may inhibit leukocyte migration and suppress inflammatory changes.

Dermatitis herpetiformis requires a regimen somewhat different from that with immunosuppression, since it generally responds well to dapsone (also

called sulfone) [12], which does not act directly in the production of pathogenic antibodies, but in the inflammatory cascade that follows the deposition of IgA. It is contraindicated for persons suffering from glucose-6-phosphate dehydrogenase deficiency (which should be tested for before treatment) because it increases the risk of hematologic side effects. Hematologic changes (anemia and meta-hemoglobinemia) are not infrequent. Hypersensitivity reactions, similar to those caused by other sulfonamides, can also occur. Previous allergy to this group of drugs contraindicates the treatment.

Unresponsive or corticodependent cases can be treated with biologicals (rituximab) or intravenous immunoglobulin, and should be referred to a specialized center.

Glossary

Acantholysis Loss of epithelial intercellular contact, showing isolated round keratinocytes.

Bullous pemphigoid Blistering dermatoses without acantholysis, caused by hemidesmosomal lesions.

Desmosome Cell structure that adheres epithelial cells to each other, composed of two plaques, one in each cell, connected by transmembranous proteins.

Direct immunofluorescence Laboratory investigation to detect antibodies in tissues.

Hemidesmosome Cell structure that adheres the basal keratinocyte to the basement membrane, composed of one plaque, also connected by transmembranous proteins.

Pemphigus group Blistering dermatoses with acantholysis caused by desmosomal lesions.

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Aphthae

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Key Points Summary
- Aphthosis is an inflammatory disease characterized by painful recurrent oral ulcerations
- The cause of aphthosis is unknown, and several studies indicate a role for the immune system in the physiopathogenesis of this disease
- Oral lesions appear mainly on nonkeratinized mucosa as painful, regular, round or oval ulcers covered with a gray pseudomembrane and surrounded by an erythematous halo
- The diagnosis of aphthosis is mainly established on clinical grounds
- Drug choice depends on the severity, recurrence rate, and response to previous therapies

Epidemiology

Aphthosis is an inflammatory disease characterized by painful recurrent oral ulcerations. It is considered the most common oral mucosal lesion, with a 3-month recurrence rate as high as 50% [1, 2]. It is more common in female patients, usually begins during childhood or adolescence, and has a tendency to diminish in frequency and severity, resolving spontaneously with age [3–5]. Incidence of aphthous ulcers has been reported ranging from 5% to 66% among different nations [1].

Etiopathogenesis

Although aphthosis is a local reaction, it is always due to a systemic predisposing factor of deregulation in the inflammatory or immune response, often undetected [6]. The cause of aphthosis is unknown, though several studies indicate a role for the immune system in the physiopathogenesis of this disease. Cytotoxicity against oral epithelial cells, decreased CD4-to-CD8 ratio, and increased CD T cells in the peripheral blood and lesions have been demonstrated, but the exact mechanism of the disorder remains to be elucidated [3, 4]

Some conditions, such as stress, hormonal changes, trauma, food hypersensitivity, systemic diseases (inflammatory bowel disease and cyclic neutropenia), hematinic deficiencies (zinc, iron, vitamin B12, and folic acid), and drugs (such as

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captopril, gold salts, nicorandil, phenindione, phenobarbital, sirolimus, tacrolimus, and sodium hypochloride) are associated with aphthae [3, 5, 7, 8] (see Box 25.1). Immunocompromised patients are known to have an increased incidence of aphthous ulcers. Human immunodeficiency virus (HIV)–associated recurrent aphthous stomatitis tends to be more severe and to last longer. Aphthosis major, the most severe variant of aphthosis, is reported to be associated with immunosuppression [4].

> **Box 25.1 Main Clinical Associations with Aphthae**
> - Physical and emotional stress
> - Infections
> - Hormonal changes
> - Food hypersensitivity
> - Immune disorder (e.g., HIV)
> - Family history
> - Sodium lauryl sulfate
> - Vitamin and mineral deficiencies: B1, B2, B6, B12, iron, folic acid, and zinc
> - Celiac disease
> - Inflammatory bowel disease
> - Antimetabolites (e.g., methotrexate)
> - Neutropenia (any cause, mainly cyclic neutropenia)

Clinical Presentation

Oral lesions appear mainly on nonkeratinized mucosa as painful, regular, round or oval ulcers covered with a gray pseudomembrane and surrounded by an erythematous halo. The presence of aphthae in keratinized sites of the oral mucosa (i.e., dorsum of the tongue, gingiva, and∕or hard palate) is more frequent in severe clinical cases.

Aphthosis can be classified as minor (lesions <10 mm), major (lesions >10 mm that heal with scarring), and herpetiform (crops of lesions <5 mm), although patients may present more than one pattern simultaneously.

Aphthae minor (Sutton's disease) is the most common form, affecting approximately 85% of aphthous patients. The ulcers are superficial, usually <1 cm in diameter (Fig. 25.1). The

Fig. 25.1 Aphthae minor. Oval ulcers surrounded by an erythematous halo. The ulcers are superficial, usually <1 cm in diameter

Fig. 25.2 Aphthae major lesions are deeper and larger than 10 mm in diameter

number of ulcers varies from one to five [4]. Aphthae minor lesions do not result in scarring and tend to heal within 10–14 days.

Aphthae major lesions are deeper and larger than 10 mm in diameter (Fig. 25.2). It affects approximately 10–15% of all cases, causing significant pain and, sometimes, dysphagia. The ulcers persist for up to 6 weeks and heal with scarring.

Fig. 25.3 Herpetiform aphthae. Multiple ulcers that may be up to 100 lesions in number. These are small in size and measure 2–3 mm in diameter

Herpetiform ulceration is characterized by recurrent crops of multiple ulcers, perhaps up to 100 in number. These are small in size and measure 2–3 mm in diameter (Fig. 25.3). Lesions may coalesce to form large irregular ulcers, which persist for about 10–14 days. Unlike herpetic ulcers, these are not preceded by vesicles and do not contain viral infected cells. This type has a later age of onset than other clinical variants of aphthae [9].

Sites of keratinized mucosa are more resistant to the onset of aphthosis. Similarly, mucosal keratinization attributable to irritative exogenous factors such as nicotine is protective [6]. Several studies reveal a negative association between cigarette smoking and aphthae [9–11].

The appearance of lesions may be acute (single episode), continuous, or subintrant according to the cause or underlying disease. Severe cases can be accompanied by genital ulceration and systemic manifestations such as fever, arthralgia, erythema nodosum, and skin pustules (complex aphthosis). Aphthosis can affect the patient for many years and should not be confused with sporadic aphthous injury, which, in general, is posttraumatic and common in young people [5, 6, 12].

The recurrent episodes of aphthosis may be triggered in susceptible individuals in the course of acute viral infections (Lipschütz ulcer), immunodeficiencies such as AIDS or transplanted patients, inflammatory bowel disease, Behçet's disease, and cyclic neutropenia, among others. It can occur simultaneously with skin disorders resulting from systemic inflammatory changes, such as erythema nodosum and pyoderma gangrenosum.

Whatever the cause and the evolution, the clinical-pathologic substrate for aphthosis is always the same.

Diagnosis

The diagnosis of aphthosis is mainly established on clinical grounds (Box 25.2). Although there is no laboratory diagnostic test, ulceration and superficial tissue necrosis, with presence of neutrophils and lymphocytes infiltrating the epithelium and the lamina propria, with variable spread and endothelial edema, supports the diagnosis. Histochemical and immunohistochemical stains for microorganisms are necessary to exclude infectious processes such as herpes and fungal infections. Salivary gland inflammation and necrosis may also be seen in cases of aphthosis major whereby deep ulceration is present.

> **Box 25.2 Diagnosis of Aphthosis**
> Painful, regular, round or oval ulcers covered with a gray pseudomembrane and surrounded by an erythematous halo on nonkeratinized mucosa.

Complementary Examinations

Blood count if differential diagnoses are suspected: Tzanck smear, histopathology, direct immunofluorescence, syphilis serology. According to presenting signs and symptoms: colonoscopy, ophthalmologic evaluation, HIV serology.

Differential Diagnosis

Herpes simplex virus (HSV) infections may have lesions similar to aphthae; however, HSV lesions are found primarily on attached keratinized mucosa, such as the hard palate or gingiva, and are preceded by vesicles. Other ulcers similar to aphthae are also seen in Behçet's syndrome, Sweet's syndrome, HIV infection, cyclic neutro-

penia, and other immunodeficiencies, and, rarely, in children in association with fever and pharyngitis (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis) [13–15].

Differential diagnoses also include varicella zoster virus infections (shingles), Coxsackie virus (herpangina and hand-foot-and-mouth disease), erythema multiforme, Wegener's granulomatosis, pemphigus vulgaris, syphilis, and mainly opportunistic infections such as orificial tuberculosis, histoplasmosis, and acute leukemia.

Therapeutic Approach

The aim of the treatment is to decrease symptoms, reduce ulcer number and size, and increase disease-free periods.

Management of recurrent aphthous ulcer requires good oral hygiene, topical steroids, dapsone, colchicine, and thalidomide. Drug choice depends on the severity, recurrence rate, and response to previous therapies.

The several topical treatments described in the literature are merely symptomatic, so that they have no influence on the course of aphthae episodes because, as already explained, the cause of aphthosis is always systemic (never local) [6].

A topical anesthetic such as 2% viscous lidocaine hydrochloride is used to palliate the pain. Caustic topical treatments that reduce pain by destroying nerve terminations are contraindicated, since they increase the ulcer size, make ulcer healing difficult, and increase the risk of secondary infection.

Mouthwashes of tetracycline and local antihistamines have a mild anesthetic effect. Topical corticosteroids (Orabase adhesive vehicles or mouthwash solution) have an analgesic effect and can be used in mild episodes.

Systemic therapy is the only effective treatment for termination and prevention of new episodes. It is crucial to control the underlying disease (bowel disease, AIDS, etc.) because aphthosis may indicate activity of these processes. In acute episodes, oral corticosteroid therapy is indicated. Medications that inhibit the onset of episodes include colchicine (0.5–2 mg/day) and dapsone (100 mg/day), which can be used alone or in combination [5, 6, 13, 16].

Thalidomide (100–300 mg/day) is the most effective therapy for severe and/or refractory cases [17]. Recently, biological therapies, such as infliximab, have been used in very severe cases [18–20].

Glossary

Aphtha Synonymous to aphthosis. Also used as the description of the individual ulcer of the disease.

Aphthosis A disease characterized by bursts of oral ulcerations, accompanied or not by ulcerations elsewhere (usually genitals) and systemic complaints.

Dapsone Diaminodiphenyl sulfone (DDS), an antibiotic used in the treatment of leprosy and as an anti-inflammatory drug in several noninfectious skin diseases.

Herpetiform ulceration One of several clinical types of aphthae, i.e., one that presents as multiple subintrant small ulcerations.

Oral ulcer Any lesion characterized by loss of the oral epithelium.

Thalidomide An immunomodulatory drug that is the prototype of the thalidomide class of drugs.

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Adverse Drug Reactions

26

Paulo Ricardo Criado

Key Points summary

In situations that involve patients with acute adverse drug reaction, certain general principles should be observed:

- If possible identify the physiopathologic mechanism involved in the reaction;
- Identify as rapidly as possible the drug inducing the reaction and always opt for its withdrawal; in some circumstances the choice is difficult as there is no alternative drug and its use is essential for the maintenance of life;
- A careful and intensive observation is recommended for the occurrence of warning signs regarding the appearance of a potentially severe adverse drug reaction, especially in relation to mucous, oral, ocular, and genital involvement and progression of any present cutaneous eruption;
- It is imperative that the drug responsible may be withdrawn on a permanent basis together with chemically related compounds, and this advice is also valid for first-degree relatives who can present the same type of reaction.

Introduction

Adverse reactions to drugs are complications that are of relevance to medicinal therapy [1]. It is estimated that 5–15% of patients treated with some medication develop adverse reactions [1].

The incidence of adverse reactions to drugs among hospitalized patients is roughly 30%, 2–3% of which constitute cutaneous reactions [1, 2]. Such reactions are seldom severe but may lead to high mortality rates [3].

In this chapter, three groups of cutaneous adverse drug reactions (ADRs) are discussed: (i) severe ADRs; (ii) moderate or mild cutaneous ADRs, and (iii) ADRs caused by chemotherapy drugs.

Severe Adverse Drug Reactions

Severe cutaneous adverse reactions to drugs (SCARDs) generally require hospitalization, sometimes in the intensive therapy or burn care unit for observation of vital signs and visceral

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function. The aim of this study is to describe these reactions in order to facilitate recognition and treatment. This group of drug reactions includes anaphylaxis, Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and, depending on the systemic involvement, erythroderma. In this chapter we approach the characteristics and treatment of some adverse reactions to drugs, including anaphylaxis, erythroderma, SJS, and TEN.

The prevalence of SCARDs is estimated at 1 in 1,000 hospitalized patients. SJS and TEN are particularly severe [4]. In general, fatal cutaneous drug-induced reactions occur in 0.1% of clinical patients and 0.01% of surgery patients [1].

SCARDs may be defined as usually requiring hospitalization, at times in intensive therapy or burn care units for close observation of vital signs and visceral function. This group of drug reactions includes anaphylaxis, SJS, TEN, drug hypersensitivity, and, depending on the systemic involvement, erythroderma, acute generalized exanthematous pustulosis (AGEP), cutaneous

necrosis induced by anticoagulants, drug-induced vasculitis, and reactions such as serum disease [4].

Quick differentiation between a SCARD and a less severe eruption may be difficult, although essential. Withdrawal of the suspected drug is the surest way of intervening to reduce mortality [4].

Most cutaneous reactions to drugs are usually observed as a morbilliform or maculopapulous exanthema [2, 5, 6]. Unfortunately, erythema morbilliform (Fig. 26.1) most often characterizes the appearance at onset in the severest of cases, including TEN, serum disease, and drug hypersensitivity syndrome [4].

Djien et al. [3], studying 133 patients with reactions to drugs clinically presenting with erythematous cutaneous eruptions (morbilliform and scarlatiniform exanthema, maculopapulous, and small isolated papules), concluded that three types of severe clinical markers exist with respect to this kind of reaction: fever, lymphadenopathy, and extensive cutaneous affection. The authors excluded specific forms from the study, such as
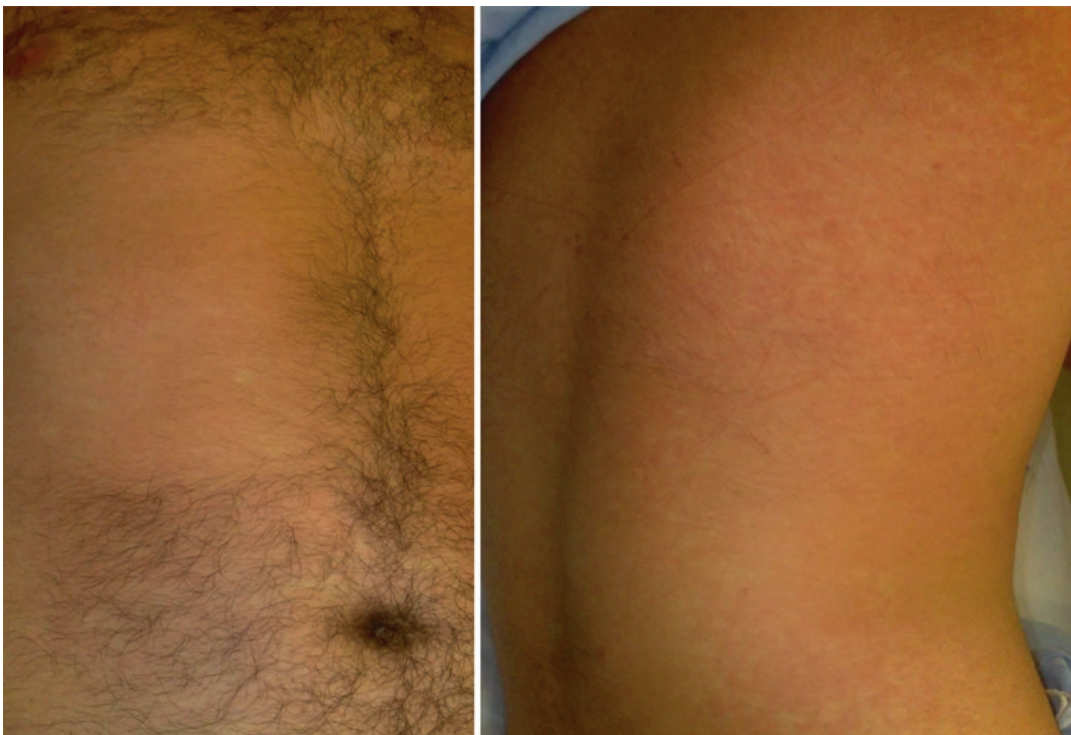
Fig. 26.1 Exanthema morbilliform

Chart 26.1 Symptoms or signs suggesting a progressive severe adverse drug reaction

Clinical findings	Mucocutaneous	Extensive erythema
		Skin pain
		Facial edema or centrofacial involvement
		Cutaneous necrosis
		Palpable purpura
		Bullous lesions or epidermal detachment
		Tongue edema or uvula edema
		Urticaria
		Positive Nikolsky sign
		Erosions on mucous membranes
	General symptoms or signs	High fever (>40 °C)
		Adrenomegaly
		Arthralgia or arthritis
		Tachypnea and or wheezing
		Hypotension
Laboratory abnormalities		Eosinophilia >1,000 mm^3
		Lymphocytosis with atypia
		Abnormalities of liver enzymes or function

SJS, TEN, fixed drug eruption (FDE), AGEP, phototoxicity, and vasculitis. This suggests that in cases of drug-induced reactions with extensive cutaneous affection, with or without lymphadenopathy, a laboratory investigation is required with a complete hemogram and hepatic function test.

In 1994, Roujeau and Stern [4] put forth clinical and laboratory criteria leading to the suspicion that a reaction to drugs could develop into more severe behavior (Chart 26.1).

We next discuss the following reactions: anaphylaxis and anaphylactoid reactions, erythroderma, and the clinical spectrum of SJS and TEN (Lyell's disease).

Anaphylaxis and Anaphylactoid Reactions

Anaphylaxis is a quick systemic reaction usually presenting a risk to life and resulting in immediate hypersensibility mediated by immunoglobulin E (IgE). Anaphylactoid reactions mimic anaphylaxis, although they are not related to immunologic mechanisms [4, 7]. These reactions lead to a powerful activation of mastocytes, with a massive release of mediators [7, 8].

Drugs are not the more important cause of anaphylaxis, as they are responsible for merely 13–20% of cases [8] .Drugs that do cause anaphylactic reactions include β-lactam antibiotics (responsible for 75% of fatal anaphylactic reactions in the United States), cephalosporin, sulfonamides, hemoderivatives, enzymes (trypsin, chymopapain, and streptokinase), insulin (very rare nowadays, owing to use of recombinant human insulin), vaccines (due to preservatives, proteic components, and gelatin; some reports of patients show sensitivity to eggs and allergic reactions to vaccines), allergenic extracts, protamine, and progesterone [7, 8].

Anaphylactoid reactions may occur with acetylsalicylic acid, nonhormonal anti-inflammatory drugs, iodide contrasts, angiotensin-converting enzyme (ACE) inhibitors, and fluorescein [7].

During general anesthesia, anaphylactic and anaphylactoid reactions may occur. These are difficult to differentiate because of the large amount of medications used, such as anesthetics, muscular relaxants, analgesics, nonhormonal anti-inflammatories, and antibiotics [7].

Their clinical emergence tends to occur suddenly, within 30-min to 1-h intervals after contact with the precipitating factor, although delayed reactions are rarer. They show an appearance of pruritus, urticaria (Fig. 26.2), rhi-

Fig. 26.2 Acute urticaria

noconjunctival symptoms, angioedema symptoms (especially laryngitis), hypotension, and lung sounds [7]. The following ailments may be observed: abdominal pain, diarrhea, vomiting, uterine contraction, and cardiac arrhythmia. After a few hours symptoms may reappear during a late phase, although this is by no means automatic [4, 7].

Patients with anaphylaxis must be identified as fast as possible, and treatment must be initiated immediately [8]. This reduces the risk of fatal reactions [8]. The following are signs of anaphylaxis that pose a risk to life: presence of stridor, edema of the glottis, intense dyspnea, lung sounds, hypotension, cardiac arrhythmia, shock, convulsions, and loss of consciousness [7, 8]. In patients using β-blockers, anaphylaxis is often severe and may be resistant to conventional treatment [8].

Various conditions must be considered in the differential diagnosis when suspecting anaphylaxis [8]: cardiac arrhythmias, acute myocardial infarction, food aspiration, convulsive disease, reaction to insulin, pulmonary embolism, syndrome etiology (e.g., the presence of carcinoid tumors or reaction to alcohol and chlorpropamide), hysterical behavior, vasovagal reactions, and fictitious allergic reactions. Vasovagal reactions are most often confused with anaphylaxis [8]. In general they are consequences of procedures such as injections, which present as a clinical condition consisting of facial paleness, nausea, profuse sweating, and syncope, with symptoms improving without treatment 20 to 30 min later [8]. Absence of pruritus in the presence of a slow pulse and normal blood pressure distinguish vasovagal reactions from anaphylaxis [8].

The treatment of anaphylaxis consists of short- and long-term measures [8]. The immediate goal is to maintain the permeability of the airways and blood pressure, in addition to administering oxygen in more severe cases [8]. Epinephrine must be administered as soon as possible, with a standard dose of 0.01 mg/kg of a 1:1,000 solution, up to a maximum of 0.3–0.5 ml, subcutaneously every 10–20 min until the patient is stabilized.

Erythroderma

This is a condition characterized by a state of generalized erythema and scaling (exfoliative dermatitis) of the skin. It has the morphologic appearance of various cutaneous diseases such as psoriasis, atopic dermatitis, T-cell cutaneous lymphoma, and reactions to drugs [9].

The dissemination of a maculopapular condition caused by medication may lead to the emergence of an erythrodermic syndrome. Various types of drug-induced cutaneous reactions (including contact dermatitis, photosensitivity, and maculopapulous reactions) would be responsible for roughly 7.3% of erythroderma cases [10].The secondary drug-induced erythroderma conditions, as opposed to erythrodermas resulting from other etiologies, most often set in quickly and also tend to regress quickly after withdrawal of the medication being used [10].

Pruritus arises 1–4 weeks after starting drug use, in association with diffuse erythema covering roughly 90% of the body surface, followed by lymphadenopathy and scaling. When acute, large amounts of epidermis are exfoliated; when chronic, it produces small elements [9] (Fig. 26.3). Pruritus and a sensation of diffuse burning occur [9].

Exfoliative dermatitis leads to systemic complications such as hydroelectrolytic and thermoregulatory disturbances, high cardiac insufficiency, tachycardia, capillary leak syndrome, and infection [11–13]. The effect of
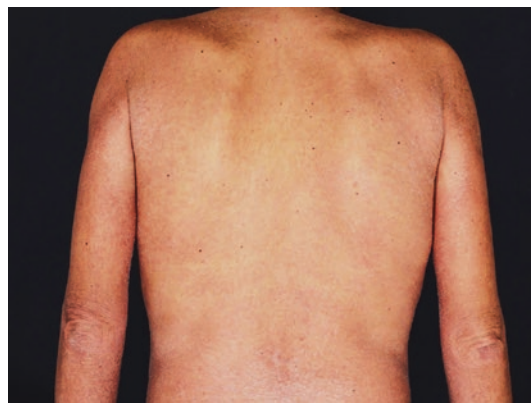
Fig. 26.3 Exfoliative dermatitis (erythroderma)

exfoliative dermatitis on the organism depends on the intensity and duration of the process [13].

Common laboratory findings in the erythrodermic state include light anemia, leukocytosis with eosinophil, high IgE, an increase of the hemosedimentation process, a drop in serum albumin, and a rise in uric acid [9, 13]. Increased IgE and eosinophil is a nonspecific finding and is found only in secondary drug-induced erythrodermas, although it might also be due to atopic dermatitis [9, 13].

Multiple cutaneous biopsies performed simultaneously on distinct points of the skin might increase the accuracy of the diagnosis of the base disease [9]. In drug reactions vacuolar alterations may be observed on the epidermis, as well as necrotic keratinocytes [9].

The initial treatment of drug reaction in an erythrodermic patient is identical to that for erythrodermas of other causes [9, 13]. Suspending the drug is the quickest way to improve the patient's condition. One ought to consider the nutritional state and hydroelectrolytic replacement, as well as administering local measures such as antiseptic baths, humid compresses on the crusts, application of soft emollients, and low-strength corticosteroids [9].

Classic oral antihistamines may be prescribed to alleviate the pruritus and anxiety. They provide the patient with a warm and humid environment so as to prevent hypothermia and improve cutaneous hydration [9, 13].

Symptoms and signs of cardiac and respiratory insufficiency may require emergency assistance and hospitalization [9]. The most aggressive and debilitating erythrodermic states may require care similar to that offered to SJS or TEN patients.

The differential diagnosis must be performed with other types of secondary erythrodermas to cutaneous diseases, such as psoriasis, contact dermatitis, seborrheic dermatitis, lichen planus, bullous pemphigoid, and pemphigus foliaceus, as well as systemic diseases such as leukemias, T-cell cutaneous lymphoma, and Hodgkin's lymphoma, in addition to erythrodermic states secondary to internal cancer [9, 13].

Clinical Spectrum of Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis (Lyell's Syndrome)

What currently exists is a combination of concepts according to which spectrum of erythema multiforme (EM), including EM minor and EM major (EMM), is separated from another spectrum of reactions, which includes SJS and TEN (Lyell's syndrome), referred to here as the SJS/TEN spectrum [14–17].

However, according to Assier et al. [18], it seems possible to separate EMM patients from true SJS patients based on clinical symptoms and disease origin. These authors define the EMM pattern as consisting of characteristic mucous erosions and cutaneous lesions (typical targets, with or without blisters), symmetrically distributed and commonly acral. SJS would be represented by mucous erosions and disseminated cutaneous purpuric macules that are frequently confluent, with a positive Nikolsky sign and epidermal scaling limited to less than 10% of the body surface [14, 18]. EM would include recurrent, postinfectious cases (especially related to herpes simplex and mycoplasma), or eventually related to exposure to medication, with a low mortality rate and without lethality. On the other hand, SJS would comprise a severe ADR with high mortality rates and a reserved prognosis for many cases [4, 14, 19].

In 1993, Bastuji-Garin et al. [19] put forward a clinical classification of the spectrum that included ME bullosa up to TEN. To better understand this classification [19], we note the characteristics of the dermatologic lesions of which the group consists, defined as follows:

- Epidermal detachment: refers to epidermal loss, which at times occurs in flaps (Fig. 26.4).
- Typical targets: lesions less than 3 cm in diameter, in disc shape, with well-defined borders, and exhibiting at least three distinct zones, namely two concentric halos around a central disc (Fig. 26.5).
- Atypical flat targets: lesions that are not raised, but are round or disc shaped, with two zones and/or borders that are not well defined.

- Atypical raised targets: round or disc-shaped lesions, palpable or raised, but without the two zones and/or well-defined borders.
- Macules/spots: erythematous or purpuric stains, irregularly shaped or confluent, with or without blisters (Fig. 26.6).

Insofar as the area of epidermal necrolysis makes up one of the two main factors of prognosis, a consensus was reached on classifying the spectrum [14, 19]: (i) SJS in cases with mucous erosions and disseminated purpuric macules and scaling of the epidermis below 10%; (ii) SJS/TEN superposition or transition in cases with epidermal scaling between 10%

Fig. 26.4 Epidermal detachment in TEN

Fig. 26.6 Purpuric macules found in TEN and SJS
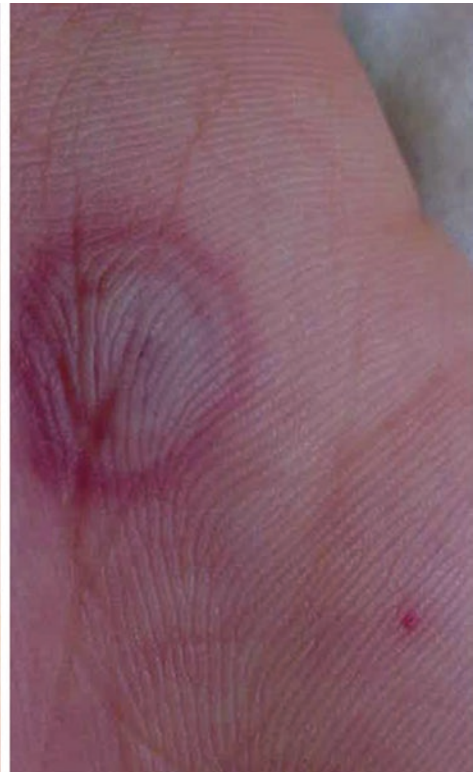
Fig. 26.5 Typical targets in the erythema multiform spectrum

and 30% of the body surface; and (iii) TEN in cases with disseminated purpuric macules and epidermal scaling above 30%; or (iv) in rare cases with disseminated necrolysis (over 10% scaling) without any of the lesions described above.

Stevens–Johnson Syndrome

SJS is an entity characterized by the presence of lesions similar to those of EM, but with purpuric macula and widely distributed blisters or even lesions in atypical targets dispersed over the dorsal aspect of the hands, palms, soles of the feet, extensor region of the extremities, neck, face, ears, and perineum; the face (Fig. 26.6) and trunk (Fig. 26.7) are prominently involved [4]. Incidence of SJS is estimated at roughly one in three cases per million residents yearly [20–22].

SJS may be preceded by a discrete maculopapulous eruption similar to exanthema morbilliform [19]. Blister formations are possible, though usually not determined by an epidermal detachment of over 10% of the body surface [4, 14, 19]. Mucous involvement occurs in roughly 90% of cases, generally on two distinct mucous surfaces; this may precede or follow cutaneous involvement [4, 14, 19]. Onset begins with enanthema and edema, which give rise to erosions and pseudomembranous formations on the eyes, mouth, genitals, pharynx, and upper airways [19]. Some 10–30% of cases occur with fever and lesions in the gastrointestinal and respiratory tracts [4]. Its prognosis seems to not be affected by the type and dose of the drug responsible, nor by human immunodeficiency virus (HIV) infection [4].

The therapeutic options for SJS are limited and controversial [4, 23, 24]. Corticosteroids are frequently used [25], although some cases have not shown a satisfactory response [24]. In agreement with most authors, the use of systemic corticosteroids on the initial SJS and TEN forms do not currently demonstrate any proven benefits. The advanced forms of this spectrum of relations

Fig. 26.7 Purpuric macules in SJS

have clearly deleterious effects on the patient [26]. The treatment and prognosis of SJS are tackled in combination with that of TEN.

Toxic Epidermal Necrolysis or Lyell's Syndrome

TEN is an entity characterized by extensive scaling of the epidermis in the wake of necrosis (epidermal necrosis) [4, 14, 15]. The term "toxic epidermal necrosis" was introduced by Lyell in 1956 [14]. Fortunately, it consists of a very rare adverse reaction to drugs. In Europe, its incidence is estimated to be at 1.1 [4] cases per million residents yearly [26].

In AIDS patients, however, the risk of this reaction does rise, estimated at one case in every 1,000 patients yearly [14]. In general, there is a slight predominance among women (1.5–2 cases in females for every male case). Indeed, the disease's occurrence in AIDS patients ends up balancing out the incidence rate between the sexes [14].
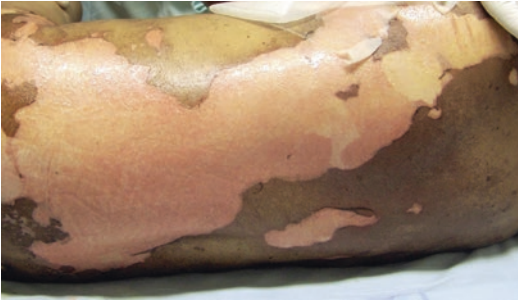
Fig. 26.8 Toxic epidermal necrolysis (TEN)

Fig. 26.9 TEN resulting from cephalexin

The initial characteristics of TEN are nonspecific influenza-like symptoms, such as fever, sore throat, coughing, and burning eyes. These are considered prodromic manifestations preceding a cutaneous and mucous affection by 1–3 days [4]. An erythematous eruption emerges symmetrically on the face (Fig. 26.8) and the upper part of the trunk, extending to the craniocaudal region and provoking symptoms of burning or painful skin [4, 14].

The individual cutaneous lesions are, for the most part, characterized by erythematous macules with poorly defined contours and a purple center. They progressively spread over the anterior thorax and back [4, 14]. Less commonly, the initial eruption may consist of an extended scarlatiniform exanthema. In roughly 2–5 days or, at times, within a few hours, or more seldom in about a week, complete extension of the cutaneous condition occurs [14]. At first, some cases may present lesions persisting in sun-exposed areas of the skin [14]. The apex of the process consists of characteristic denuding of the necrotic epidermis, standing out as veritable red strips or flaps on the areas affected by the base erythema (Fig. 26.9) [4, 14].

The epidermis is raised by the serum content of flaccid blisters, which are progressively confluent and provoke rupture of the blisters and detachment of the skin. This causes an aspect of severe burns on the patient's skin, with the skin denuded, bleeding, and with an erythematous-purple color, as well as continued elimination of serosity, which contributes to hydroelectrolytic unbalance and accentuated protein loss [4, 14]. The Nikolsky sign is positive over widespread areas of the skin [4, 14].

The areas of the skin subjected to pressure, such as the lower shoulders, back, and buttocks, are the first to release epidermal flaps [4, 14]. Cutaneous extensor affection might determine a state of acute cutaneous failure [15, 27]. The cutaneous surface can virtually be 100% affected, although scalp affection is exceptional [14].

The mucous membranes are affected in 85–95% of patients, commonly preceding skin involvement by a day or two [14]. In the order of frequency, the disease afflicts the oropharynx, eyes, genitalia, and anus [14]. Extensive and painful erosions lead to labial crusts, salivation, feeding obstruction, photophobia, and painful urination and evacuation [14].

Severe eye sequelae, with the formation of synechiae between the eyelids and conjunctiva by pseudomembranous conjunctival erosions, and blindness may occur [4, 14]. Ceratitis and corneal erosions have been reported, as well as a secondary sicca-like syndrome [14].

High fever or hypothermia may occur because of a thermoregulatory imbalance until complete healing, even in the absence of concomitant infections [14]. The abrupt drop in temperature is more indicative of sepsis than of fever itself [14]. Psychomotor agitation and

mental confusion are not uncommon, and usually indicative of hemodynamic complications and sepsis [14]. Many internal organs are affected by the same pathologic process that involves the skin and determines a spectrum of systemic manifestations [4, 14].

Systemic involvement occurs, causing erosion in the esophagus and gastrointestinal tract, which may progress to esophageal constrictions, transaminase increases in 50% of cases (hepatitis in 10%), pseudomembranous colitis, and pancreatitis [23]. In the respiratory tract tracheobronchial erosions and secondary pulmonary interstitial edema, with the correction of hypovolemia, can be found [15]. Anemia can be constantly observed, as well as lymphopenia in up to 90% of patients [15]. Thrombocytopenia is found in 15% of patients; neutropenia occurs in 30% of cases, and when present indicates a worse prognosis [15, 23].

The medications most commonly causing TEN are sulfas, phenobarbital, carbamazepine, dipyrone, piroxicam, phenylbutazone, aminopenicillin, allopurinol, and nevirapine. However, it is necessary to consider that new drugs are continually being reported as triggering TEN [4, 14, 15, 23].

Considerations on the Physiopathology of SJS and TEN

The exact mechanism by which SJS and TEN develop is not well defined.

Some authors have suggested the participation of the altered metabolism of drugs with the predominance of a slow acetylator genotype in SJS and TEN patients, and a deficiency in the mechanisms involved in detoxification of reactive intermediary metabolites [28–30].

In addition to the metabolic mechanisms, there is evidence to suggest that, especially in TEN, the epidermal necrosis is mediated immunologically [4, 14, 30]. It is known today that SJS and TEN are disturbances mediated by T cells, similarly to acute graft-versus-host disease (GVHD), with cytotoxic T cells being responsible for the epidermal necrosis through an apoptosis in keratinocytes [14, 30].

Posadas et al. [31] have shown the association of high tumor necrosis factor α (TNF-α) levels with the severity of the reaction. This cytokine has been related to an induction in the adhesion and activation of T cells and monocytes. It also participates in apoptosis, irrespective of the action of perforins [31]. It has been demonstrated also that apart from TNF-α, the perforins granzyme B (GRB) and Fas ligand (FasL) are found to be high in the initial stages of a drug reaction, particularly in SJS and TEN. This reinforces the hypothesis of the participation of cytotoxic mechanisms [31]. Nowadays, cytotoxic reaction caused by granulosin liberation from T cells is the major mediator involved in cell apoptosis, and the spectrum of SJS/TEN is grouped in Type IVc of immune reactions, as classified by Pichler.

Correia et al. [32] have observed a similar seric cytokine profile between TEN and acute GVHD. These authors showed a significantly high serum level of interleukin (IL)-6 and IL-10 in TEN and acute GVHD patients as opposed to normal blood donors [32]. IL-6 is a multifunctional proinflammatory cytokine produced by various cells, including keratinocytes. It consists of a main circulating endogenous pyrogen [32]. This explains the presence of fever that is unrelated to the infection in the first days of TEN and GVHD [32]. In turn, IL-10 is an endogenous antipyrogen agent. It is produced by keratinocytes with the purpose of blocking inflammatory cytokines such as IL-1, IL-6, and TNF-α, in addition to being a powerful suppressant of macrophage, T-cell, and natural killer cell functions [32].

By contrast, as IL-10 recruits CD8+ lymphocytes from the peripheral blood, its increase in blister fluid explains the high number of these cells in patients' epidermis [32] .The elevation of IL-10 creates a natural mechanism against excessive tissue inflammatory reaction [32].

Chosidow et al. [33] have suggested that the cellular cytotoxic targets are viral antigens with a potential to alter immune responses resulting from exposure to medications.

Considerations on Treating SJS and TEN

Treatment for SJS and TEN patients is similar to that for patients who have suffered extensive burns, with a number of rare exceptions [23]. All patients have to submit to cutaneous biopsy to confirm the diagnosis [23]. The patient must be observed in an intensive therapy unit, in an isolated and heated environment so as to avoid any cutaneous trauma [4, 14, 23]. The treatment must proceed by suspending any drug that is not essential to the patient's life and begin replacement of intravenous fluid, mainly when an oral mucous lesion obstructs liquids from being ingested [4, 14, 23]. Isolation and feeding must be carried out through the nasogastric probe because the patient shows calorie and protein loss [4, 14, 23].

Corticosteroids should only be administered within 48 h of the condition's onset. It has not proved to be beneficial after this period because of its delaying epithelialization and increasing protein catabolism, in addition to increasing the risk of infection [23, 26].

Antibiotic therapy has to be administered to cases whereby a sudden drop in temperature occurs and with a concomitant drop in the general status or increase of cultivated bacteria on the skin with a predominance of a single strain [23, 26]. It must be emphasized that during the first days, the most common infections are by *Staphylococcus aureus* and later by Gram-negatives (*Pseudomonas aeruginosa*) or *Candida albicans* [23].

Noncontrolled reports and studies on the treatment of TEN exist, reporting the use of intravenous immunoglobulin, cyclosporine, cyclophosphamide, plasmapheresis, and anticytokine monoclonal antibodies, among others, in an attempt to curb the process of epidermal necrosis. The value of these studies has been questioned, however, particularly owing to the fact that in most patients who are hospitalized the phenomenon of necrosis virtually comes to a halt [15].

Prins et al. [34] published a multicenter, retrospective study on intravenous immunoglobulin use in treating TEN patients, which obtained excellent results. A 48-patient cohort, average age 43 years (±24) and consisting of 24 women and 24 men, with a 10–95% variation of epidermal detachment of the total body surface area, was treated. Mucous membrane was affected in 91.7% of these patients. The patients received intravenous infusion of gammaglobulins begun on average 7 days after onset of TEN (with a variation of 2–30 days). It was administered over a period of 1–5 days, in doses varying from 0.65 to 5.8 g/kg (mean total dose of 2.7 g/kg). An objective positive response to treatment occurred with a break in the progression of TEN, observed in 43 (90%) of the 48 patients. In all there were six deaths. The authors concluded that early use of intravenous gammaglobulin is safe, with a recommended dose of 1 g/kg daily for 3 days in a row. In contrast to the studies of Prins et al. [34], a French group (Bachot, Revuz, and Roujeau) led a noncomparative prospective study of 34 patients diagnosed with SJS (nine patients), SJS/TEN overlapping (five patients), and TEN (20 patients). They concluded that intravenous gammaglobulin in a 2-g/kg daily dose, administered for 2 days in a row, did not reduce patient mortality [35].

Until such discrepancies in the results have been cleared up, intravenous gammaglobulin use in treating TEN will remain controversial [36]. However, as the volume of data encourages its application and effective alternative therapies remain lacking, it seems difficult to not suggest a high dose of intravenous gammaglobulin, especially as a way of intervening early in quickly progressing TEN cases.

Considerations on the Prognosis

Whereas mortality rate is low for EMM (<1%) and SJS (roughly 5%), it is above 40% for TEN patients with macules [37]. The mortality rate

Chart 26.2 SCORTEN grade for TEN prognosis on hospital admission

Prognostic factors	Parameters	Estimated mortality related to point score
Age	≥40 years old	1 (3.2%)
Heart frequency	≥120 bpm	2 (12.2%)
Cancer presence	Yes (1 point); No (0 points)	3 (35.5%)
Percent of epidermal detachment over total body area	>10%	4 (58.3%)
Serum urea (BUN)	>28 mg/dl or >10 mmol/l	≥5 (90.0%)
Serum bicarbonate	<20 mEq/l	
Serum glucose	>14 mmol/l (or >252 mg/dl	

rises with age range and increased surface area of the epidermal scaling [37].

We reiterate the classification methodology adopted by multicenter studies, prospectively named SCARD (Severe Cutaneous Adverse Reactions). The results of the latter were recently published based on the analysis of 552 patients and 1,720 controls [38]. This classification system (named SCORTEN) is summarized in Chart 26.2.

Despite the large range and amount of drugs that may pose a great risk of contracting SJS and TEN, an annual risk rate of five cases per year among medication users has not been exceeded [39, 40].

Drug Hypersensitivity Syndrome: DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) [41–43]

DRESS syndrome is an acronym derived from the term "Drug Rash with Eosinophilia and Systemic Symptoms" coined by Bocquet et al. Also known as drug-induced hypersensitivity syndrome (DIHS), it was first recognized in 1950 by Chaiken in a patient using an anticonvulsant. There are many synonyms used, most of them referring to the origin of the drugs involved in the drug reaction, such as dapsone syndrome, allopurinol hypersensitivity syndrome or the anticonvulsant hypersensitivity syndrome. Although a

dermatosis is usual in DRESS, the extent of skin involvement is variable and therefore the "R" in DRESS was subsequently changed from "rash" to "reaction."

Clinically, in its complete form, this syndrome includes an extensive mucocutaneous rash, fever, lymphadenopathy, hepatitis, and hematologic abnormalities with eosinophilia and atypical lymphocytes, and may involve other organs with eosinophilic infiltration, producing damage in several systems, especially in kidney, heart, lungs, and pancreas. This multivisceral involvement differentiates DRESS from other common skin reactions to drugs. Another unique feature of this syndrome is its late onset in relation to the period of introduction of the causative drug, i.e., at around 3 weeks to 3 months, and its possible persistence or worsening despite the withdrawal of the offending drug.

Incidence

The incidence of this syndrome is estimated to vary from one case among 1,000–10,000 drug exposures. Adults are more affected than children, and although the precise incidence of drug reaction has not yet been determined, it is much more common than SJS, which has an incidence of 1.2–6 cases per million person-years, and most cases are sporadic, with no gender predilection. Recognition of this syndrome is of paramount importance, since the mortality rate is about 10–20% and a specific therapy may be necessary.

Etiopathogenesis

The exact mechanism of DRESS/DIHS remains to be determined but, in cases related to anticonvulsant drugs, three components are considered: (i) deficiency or abnormality of the epoxide hydroxylase enzyme that detoxifies the metabolites of aromatic amine anticonvulsants (metabolic pathway); (ii) associated sequential reactivation of herpesvirus family; and (iii) ethnic predisposition with certain human leukocyte antigen (HLA) alleles (immune response).

Drugs Involved and Metabolism

This type of reaction is most commonly seen using seven different drug groups: (i) anticonvulsants, such as the aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital, primidone), mexiletine, lamotrigine, valproate, ethosuximide, and zonisamide; (ii) antidepressants (desipramine, amitriptyline, fluoxetine); (iii) sulfonamides and sulfones (dapsone, sulfasalazine, trimethoprim-sulfamethoxazole, salazosulfopyridine); (iv) anti-inflammatory drugs (piroxicam, naproxen, diclofenac, sundilac, phenylbutazone, ibuprofen); (v) anti-infectives (abacavir, cidofovir, terbinafine, nevirapine, minocycline, linezolid, doxycycline, telaprevir, nitrofurantoin, zalcitabine, spiramycin, metronidazole, piperacillin-tazobactam, ceftriaxone); (vi) angiotensin-converting enzyme inhibitors (captopril, enalapril); and (vii) β-blockers (atenolol, celiprolol). Cases have been reported with allopurinol, gold salts, thalidomide, calcium channel blockers (diltiazem), ranitidine, sorbinil, azathioprine, dobutamine, methimazole, propylthiouracil, and efamizulab.

The cases more consistent with DRESS/DIHS were caused by aromatic anticonvulsants, dapsone, salazosulfopyridine, allopurinol, and minocycline. Other drugs causing less typical cases are reported in the literature, but less frequently. Aromatic anticonvulsants have an estimated occurrence of DRESS/DIHS of one case for every 5,000 people exposed to the drug, and the reaction is especially common among black patients. The aromatic anticonvulsant drugs that have been associated most frequently with DRSS/DIHS are phenytoin, phenobarbital, and carbamazepine. However, newer anticonvulsant medications also containing aromatic structure (felbamate, oxcarbazepine, zonisamide, and lamotrigine) can also be involved, and the cross-reactivity between the various aromatic anticonvulsant drugs is well documented, varying between 40% and 80%. Nonaromatic anticonvulsant drugs (topiramate, levetiracetam, tiagabine, ethosuximide, valproic acid, and gabapentin) appear to be safe.

Cacoub et al. recently reviewed the literature of published cases of DRESS and found 44 drug-related out of 172 case reports published in the literature in PubMed/MEDLINE from January

Chart 26.3 Drugs reported as possible cause of DRESS/DHIS

Drugs related to DRESS
Abacavir
Allopurinol
Amoxicillin plus clavulanic acid
Amitriptyline
Atorvastatin
Aspirin
Captopril
Carbamazepine
Cefadroxil
Celecoxib
Chlorambucil
Clomipramine
Clopidogrel
Codeine phosphate
Cotrimoxazole/cefixime
Cyanamide
Dapsone
Diaphenylsulfone
Efalizumab
Esomeprazole
Hydroxychloroquine
Ibuprofen
Imatinib
Lamotrigine
Mexiletine
Minocycline
Nevirapine
Olanzapine
Oxacarbamazepine
Phenobarbital
Phenylbutazone
Phenytoin
Quinine and thiamine
Salazosulfapyridine
Sodium meglumine ioxitalamate
Sodium valproate/ethosuximide
Spironolactone
Streptomycin
Strontium ranelate
Sulfasalazine
Sulfamethoxazole
Tribenoside
Vancomycin
Zonisamide

1997 to May 2009. In about one-third of cases, the aromatic anticonvulsant drugs were more related to the onset of ADR (Chart 26.3).

Some patients experience a prodrome of flu-like symptoms about 4 weeks before the clinical reaction. There are reports of DRESS/DIHS even in patients using anticonvulsants for about 40 years.

The pathogenic mechanism of idiosyncratic reactions to drugs, such as DRESS/DIHS, has not been fully elucidated. Sullivan and Shear proposed a multifactorial model for the pathogenesis of DRESS/DIHS. Its occurrence would be determined by the combination of exposure to a drug capable of causing adverse reaction given in sufficient dosage and period of use to a susceptible patient.

A certain group of drugs associated with DRESS/DIHS, including the aromatic anticonvulsants, is metabolized to reactive oxygen intermediates that appear to be inefficiently detoxified in patients with acquired or pharmacogenetic variations in the metabolism of these drugs.

Aromatic anticonvulsants such as carbamazepine, phenytoin, and phenobarbital are metabolized by the hepatic cytochrome P450 enzymes and undergo oxidation by aromatic hydroxylation, with subsequent formation of arene oxides. Arene oxides are toxic reactive intermediates that are normally enzymatically converted to nontoxic metabolites by epoxide hydroxylase or glutathione transferase. In addition, spontaneous conversion to nontoxic phenol derivatives can occur. In cases of defective or deficient epoxide hydroxylase, arene oxides can accumulate and cause direct cellular toxicity or immune response (Fig. 26.10).

Drug interactions can be important in this syndrome. Concomitant use of lamotrigine and valproic acid increases the occurrence of the syndrome. It is thought that the mechanism for this drug interaction is the competition between valproic acid and lamotrigine for hepatic metabolism by glucuronidation, which doubles the half-life of lamotrigine and predictably would increase the possibility of adverse effects.

Positive patch tests and testing of blast transformation of lymphocytes indicate the presence of an immune reaction in which T cells participate in specific core function. Clones of drug-specific T cells have been isolated from patients sensitive to carbamazepine and lamotrigine.

Sequential Reactivation of Herpesvirus in DRESS/DIHS

Several clinical similarities that could be observed between DRESS/DIHS and infectious mononucleosis (IM) have led researchers to implicate a possible range of viruses as triggers for this syndrome. In addition, unique features of this syndrome are its late onset in relation to the period of introduction of the causative medication and frequent clinical and laboratory deterioration, as well as episodes of exacerbation despite the withdrawal of the offending drug, so that these characteristics are not necessarily typical of a reaction of specific drug etiology.

Although there are conflicting views on the pathogenesis of DRESS/DIHS in different parts of the world, recent studies have suggested a close relationship between human herpesvirus 6 (HHV-6) and the development of DRESS/DIHS.

Sporadic reports have shown that not only HHV-6, but also other herpesviruses such as HHV-7, Epstein–Barr virus (EBV), and cytomegalovirus (CMV), can be reactivated during the course of the DRESS/DIHS.

Results obtained with analysis by polymerase chain reaction showed that various herpesviruses are sequentially reactivated during the course of DRESS/DIHS in most patients. The cascade of viral reactivation is initiated by EBV or HHV-6 and extends over a period to HHV-7 and eventually to CMV [1]. In some patients, the clinical manifestations of this syndrome persist despite discontinuation of the drug involved, coinciding with the reactivation of herpesvirus, as shown in Fig. 26.11.

The reactivation of HHV-6 is evidenced by increases in the titers of IgG anti-HHV-6 DNA levels, and HHV-6 is commonly found in the second or third week after the onset of rash, despite the high variability of clinical manifestations among patients with this drug reaction. Since the reactivation of HHV-6 can be detected only in patients with DRESS/DIHS, but not other ADRs, in Japan this diagnostic test has become sensitive and specific for the diagnosis of all patients with DRESS/DIHS [7]. The detection of HHV-6 reactivation seems to be the gold-standard diagnostic test for DRESS/DIHS in Japan, with other Asian countries and Europe helping to confirm the identification of this condition.
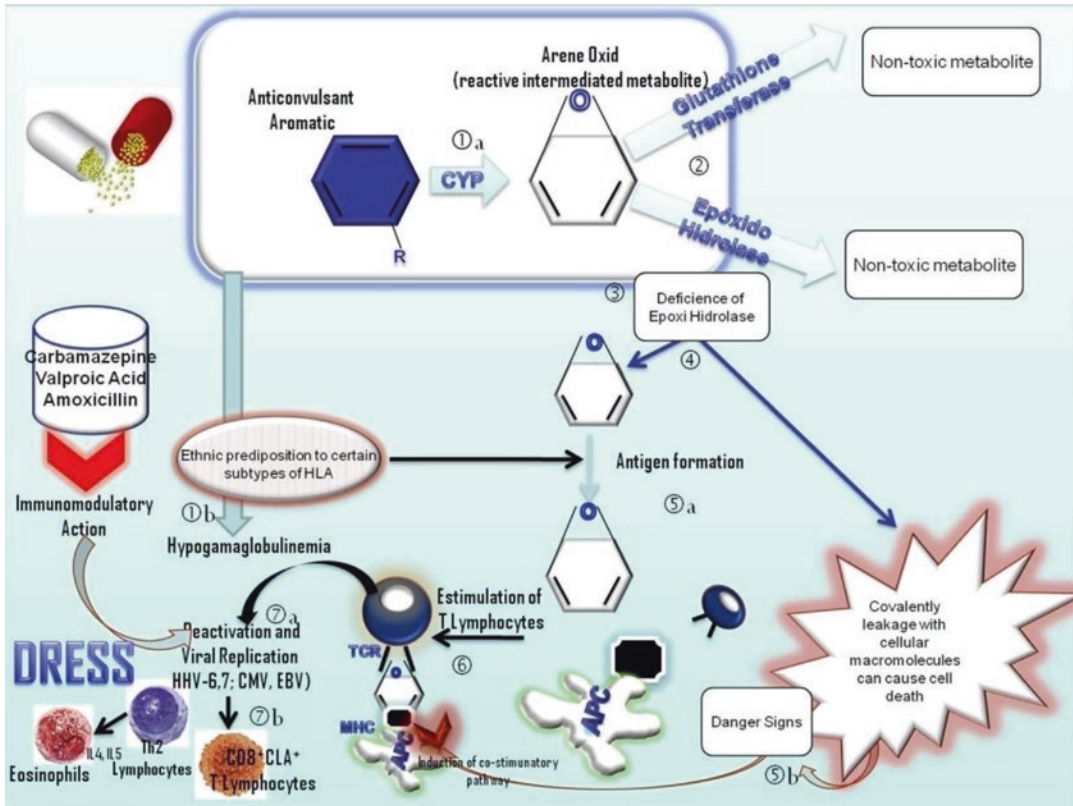
Fig. 26.10 Sequence of events of drug-virus-immune system interaction in patients with DRESS/DIHS triggered by aromatic anticonvulsants. Aromatic anticonvulsants are metabolized by the oxidation system of cytochrome P450 in arene oxide radicals (intermediate reactive metabolite). (*1a*) These arene oxides are detoxified by glutathione transferase and epoxide hydrolase in nontoxic metabolites. (*2*) In genetically predisposed individuals or by additional factors, an impaired detoxification and accumulation of these metabolites occur (*3*), which can cause cellular damage generating danger signs that can stimulate resting T cells, inducing costimulatory pathways (*4*). In addition, ethnic predisposition to certain HLA types may contribute to the formation of neoantigens from the combination of these intermediary reactive metabolites with tissue macromolecules and formation of haptens (*5a*), which can be presented via the human histocompatibility complex class I (HLA-DR) or class II (HLA-A, -B or -C), to CD4 or CD8 T cells (*6*). It was demonstrated that carbamazepine, valproic acid, and amoxicillin are able to exert immunomodulatory actions by inhibiting histone decarboxylase on B lymphocytes, producing a hypogammaglobulinemia that precedes the clinical onset of DRESS/DIHS. The clonal expansion of T cells requires sequential reactivation of latent herpesvirus, and at the same time CD8$^+$ CLA$^+$ T cells are produced, which are directed toward skin, CD8$^+$ CCR4$^+$ T cells addressed to the lungs (*7b*), and CD4$^+$ IL-4, IL-5 producer and IL-17 CD4 Th17$^+$ producer that cause tissue and peripheral eosinophilia

However, it is still unknown how detection of the viral genome in peripheral blood reflects the true status of viral reactivation in progress in many different organs and systems. Specifically, it is possible that in different compartments and organs such as spleen and lymph nodes, different herpesviruses can reactivate in sequential order completely independent of what occurs in the blood, which would explain why blood samples negative for the viral genome are obtained during the clinical activity of DRESS/DIHS.

What remains unclear is the role of herpesvirus in early DRESS/DIHS. There are two possibilities:

(i) DRESS/DIHS began as an "allergic" immune reaction to a particular drug, which seems to possess an innate ability to stimulate T cells.
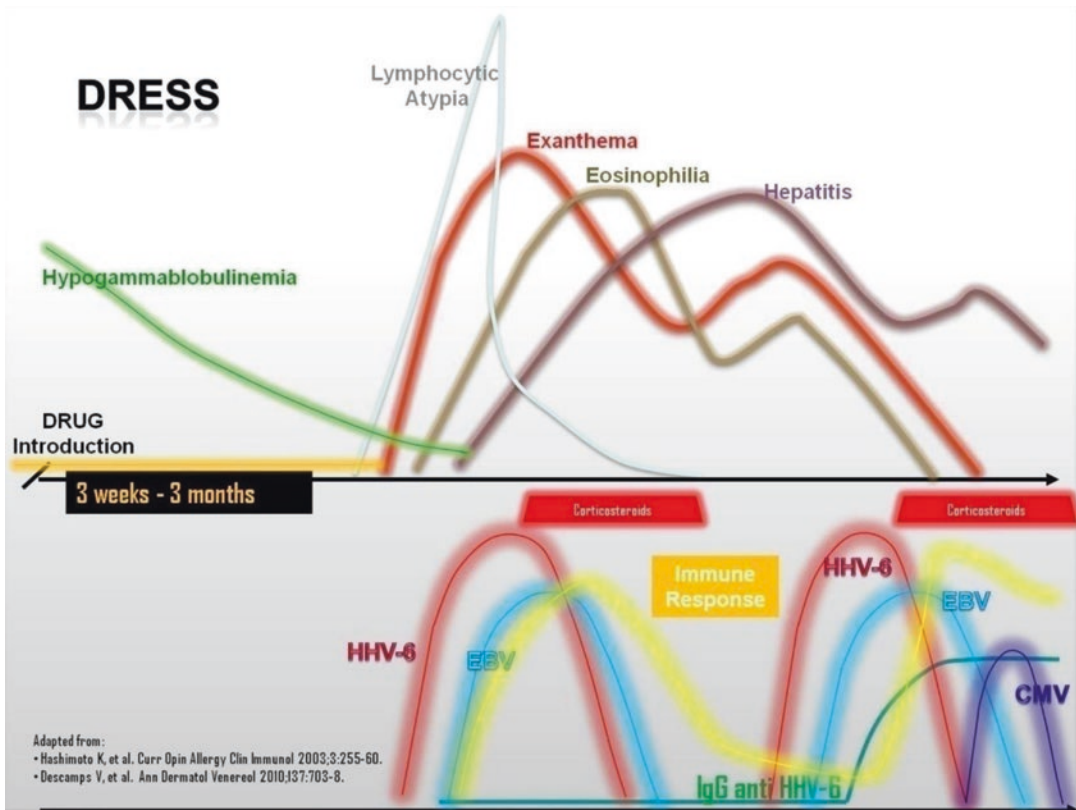
Fig. 26.11 DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)/DHIS: successive events since drug exposure, symptom onset, and viral replication

In the context of T-cell activation is a massive activation of herpesvirus housed in these cells, since the stimulation of T cells by the drug may reactivate the viral genome into the cell. Thus, the drug in turn can activate a specific cellular and humoral immune response to herpesvirus. This could explain why different herpesviruses are activated and because in another intense immune process, so-called GVHD, a similar reactivation can be observed.

(ii) The viral reactivation can occur but is initially clinically unapparent. However, T cells stimulated by virus present significant cross-reactivity with certain drugs, and exposure to these drugs leads to an expansion of T cells specific to the drug (and viruses), which persists even after drug withdrawal due to persistence of viral antigens. The simultaneous appearance of multiple concurrent viral reactivation could be explained by the ability of

HHV-6 and HHV-7 counterparts to reactivate virus. Thus, if the symptoms of DRESS/DIHS are mediated by both the various gene products and herpesvirus immune responses to viral replication, the frequent deterioration or the several exacerbations that occur despite withdrawal of the offending drug could derive, at least in part, from the sequential activation of this herpesvirus.

The viral reactivation may provide a "danger signal" (danger sign) that stimulates massive clonal expansion of both CD8^{+} and CD4^{+} non-specific T cells and causes the complete development of the syndrome. Shiohara et al. proposed the possibility that the clinical symptoms during the course of evolutionary DRESS/DIHS do not seem to be only mediated by oligoclonal expansion of drug-specific T cells, but also by antiviral T cells that cross-react with drugs.

Therefore, necessary for the occurrence of DRESS/DIHS are: (i) drugs; (ii) the virus; and (iii) their interrelationship with the immune system. A genetic predisposition has been linked to DRESS/DIHS.

How is HHV-6 acquired? HHV-6 infects almost all humans around 2 years of age. Most infections arise through the exchange of infected saliva during the first year of life, although perinatal transmission can occur. It was demonstrated that the DNA of HHV-6 can be integrated into the host DNA, and once part of the human DNA, congenital transmission can occur [7]. This was also demonstrated in the course of the DRESS/DIHS.

The temporal relationship between onset of drug use and the onset of DRESS/DIHS (3 weeks to 3 months) suggests that viruses have no primary function in the syndrome, favoring primary pathogenesis related to drug allergy.

Immune Aspects Involved in DRESS/DIHS

Patients with DRESS/DIHS have decreased total serum IgG, IgA, IgM, and B-lymphocyte count at onset, while there is an expansion of memory T cells that cross-react with both drug and virus. It is noteworthy that the lymphocyte transformation test is negative in the first week of illness and remains negative in 90% of patients 2 weeks after the onset of symptoms, becoming positive only 5–7 weeks after the initial drug reaction. This could be due to the expansion of regulatory T cells (which suppress the proliferation of memory T cells) in the early stages of the disease and its subsequent reduction by apoptosis.

Several cytokines are increased during DRESS/DIHS. In particular, levels of TNF-α and IL-6, which are typically proinflammatory cytokines, are elevated in this syndrome before the reactivation of HHV-6. Interestingly, IL-6 becomes undetectable during viral replication and increases again after the infection in most patients.

DRESS/DIHS is an entity distinct from other serious ADRs because of the dynamic changes in the immune response observed during the course of the disease. The phenotype of circulating CD4+ T cells is changed to CD8+ phenotype at the time of viral reactivation. Regulatory T cells are initially increased in number in the circulation and skin, but decrease in parallel the function of the different organs or systems.

The reactivation of HHV-6 is considered a condition requiring immunosuppression, demonstrated on several immune abnormalities in the early syndrome: marked decrease of serum immunoglobulins, the number of circulating B cells, and regulatory T-cell dysfunction.

Moreover, the participation of skin inflammation may be involved in the induction of immunosuppressive conditions. Sugita et al. demonstrated a reduction in the number of plasmacytoid dendritic cells (pDC) in peripheral blood of patients, but an increase in the expression of these cells in skin affected by the rash. The pDC human leukocyte subtypes are capable of producing large amounts of interferon-α (IFN-α), which induces the maturation of B cells in order to produce IgG and plays a critical role in antiviral defense. The pDC from circulation may accumulate in the skin and thus reduce the number of pDC in the circulation. Therefore, antiviral responses may be reduced, facilitating viral reactivation in peripheral blood and tissues other than the skin.

Although the terms DRESS and DIHS are often and mistakenly used interchangeably, there is currently a tendency to believe that the DIHS represents the most severe cases of DRESS, with reactivation of HHV-6 detected in a large majority of patients and only in a limited number of patients with DRESS [6].

Associations of HLA Alleles with DRESS/DIHS and Maculopapular Eruption Induced by Aromatic Anticonvulsants or Other Drugs (Pharmacogenomics)

The most popular hypothesis to explain the immunoallergic reactions to drugs is the theory of hapten/pro-hapten: according to this hypothesis, the drug (or metabolite) is processed by antigen-presenting cells (APCs) and expressed in the cell membrane in the context of HLA-A, -B, or -C type I (MHCI) or HLA-D type II (MHCII). The complex HLA drug (hapten) is presented to

native T cells (naive) via their T-cell receptor (TCR), which initiates different types of immune responses, depending on the HLA expressed on the APC and the cytokine environment.

The story of "HLA–drug" correlation truly began in the twenty-first century with abacavir. In 2002, two independent groups observed the abacavir hypersensitivity syndrome and that this was restricted to the allele HLA-B*5701, which conferred an elevated odds ratio (>100). GlaxoSmithKline (London, UK) led the largest international randomized pharmacogenetic clinical trial to date, which demonstrated the correlation between abacavir hypersensitivity reactions and patients with this allele, and proved that the exclusion of abacavir introduction to the patients with this allele resulted in the disappearance of the syndrome, which was first seen in 5% of patients overall who received the drug during the first weeks of antiretroviral treatment. This allele test is now routinely used before the introduction of abacavir in several countries.

The HLA alleles have a high negative predictive value but low positive predictive value in relation to ADRs, indicating that these biogenetic markers are necessary but not sufficient to trigger the allergic immune reactions. According to the theory of HLA–drug (hapten), the complex hapten only triggers an immune-allergic reaction in the presence of a specific HLA allele.

Thus, prospective HLA screening should prevent some patients from having serious idiosyncratic reactions such as DRESS/DIHS, SJS, and TEN if they have a specific risk allele by not receiving the drug related to it. HLA pharmacogenomics is a recent field of study that has been rapidly developed and implemented into clinical practice and has improved drug prescription, which is likely to become more and more important in coming years.

Besides causing SJS and TEN, carbamazepine also induces other types of ADRs, including maculopapular exanthema (MPE) and DRESS/DIHS. The association between HLA-B*1502 and carbamazepine-induced MPE was not detected in populations of ethnic Han Chinese and Hong Kong or Thai populations. Studies involving 18 Han Chinese residents in Taiwan and 56 Caucasians showed no association between cases of DRESS/DIHS caused by carbamazepine and HLA-B*1502. These data indicate that the association between HLA-B*1502 and cutaneous ADRs induced by carbamazepine are specific to SJS/TEN.

Kano et al. showed that in four of their 13 Japanese patients (30.8%) with DRESS/DIHS in whom reactivation of HHV-6 was proved, the syndrome was triggered by aromatic anticonvulsants (carbamazepine in ten, phenobarbital in two, and phenytoin in one) had HLA-B*1301. The frequency of this allele was much higher than in the Japanese population (1.3%). Although this difference was not statistically significant after correction for multiple comparisons, the authors proposed that the presence of certain alleles of HLA-B on the reactivation of the virus contributed, at least in part, to the association of HLA-B allele with DRESS/DIHS.

Kashiwagi et al. demonstrated a significant association between adverse skin reactions to carbamazepine and HLA-A*3101 among 22 Japanese patients, including erythema multiforme, erythroderma, DRESS/DIHS, SSJ, and other drug reactions. Eleven of these patients (50%), including two patients with SJS and others, were carriers of HLA-A*3101 and allele frequency was much higher in these patients (25%) than in the Japanese population (7.1%) ($p = 4 \times 10^{-4}$, odds ratio (OR) = 4.33).

In a case-control study in a Han-Chinese population a strong association between the presence of HLA-B*5801 and SJS/TEN, or DRESS/DIHS triggered by allopurinol among 51 patients (100%) was found, compared with 20 out of 135 (15%) allopurinol-tolerant patients and 19 out of 93 controls (20%) (p (Pc value $4.7 \times 10(-24)$, OR = 580).

Japanese patients with different clinical types of cutaneous ADRs caused by allopurinol, including SJS, TEN, and DRESS/DIHS, had the same HLA-B*5801 allele.

Pirmohamed et al. found an increased frequency of HLA-DR3 and HLA-DQ2 in a group of patients with carbamazepine-induced DRESS/DIHS (respectively $p = 0.01$, OR = 3.3; $p = 0.04$, OR = 2.7). It was demonstrated that activation of CD4+ T cells with IL-2 is essential for the spread

of HHV-6 in vitro. Genotyping of patients revealed that they had positive HLA-DR3 (DRB1*0301) and HLA-DQ2 (DQB1*0201).

Thus, in recent years increased attention has been given to genetic factors as a cause of variation in both the interpersonal effectiveness and adverse effects of medicines. Idiosyncratic reactions are often mediated through immune, usually severe, and unpredictable course. The main region of human DNA with genetic variations that predispose to drug hypersensitivity reactions is the region HLA. This region harbors the gene locus of most diseases and contains many genes associated with immune functions.

Although strong associations have been demonstrated between certain HLA alleles and some types of adverse skin reaction to drugs, there is no definitive evidence or published data concerning the functions involved in these alleles. The activation of T cells restricted to HLA is necessary for the induction of immune reactions and, moreover, there is the possibility that some HLA proteins have high binding affinity combined with other drugs or a metabolite of the drug through covalent and noncovalent mechanisms. On the other hand, a protective effect of HLA has also been suggested. Alfirevic et al. reported a potential protective effect of HLA-B*0702 against severe adverse skin reactions induced by carbamazepine in Caucasian patients.

The implications of pharmacogenomics are varied; one example is the recommendation of the US Food and Drug Administration (FDA), which currently recommends genetic testing for users of more than ten drugs currently marketed in that country.

Histopathology

Histopathology of the skin shows a diffuse, dense superficial and/or perivascular lymphocytic infiltrate. Eosinophils in the dermis or swelling may or may not be present (Fig. 26.12a). On some occasions there is a band-like infiltrate with atypical lymphocytes simulating epidermotropism such as mycosis fungoides.

Fernando et al. described a patient with DRESS/DIHS triggered by carbamazepine whose rash biopsy presented an unusual form of superficial perivascular inflammatory infiltrate, in which tiny granulomas along with a moderate number of lymphocytes were found. The authors speculated that granuloma formation may be due to a sustained exposure to the drug, even after the onset of DRESS/DIHS. The expansion of CD4+ T cells producing IFN and other cytokines results in recruitment of macrophages which, as a result of maintained exposure to the drug and persistence of cytokine release, promote differentiation into epithelioid cells, which then secrete TNF to promote fusion of these cells into multinucleated giant cells.

Thus, biopsies of organs involved in DRESS/DIHS, such as skin and liver, on a significant number of patients may demonstrate the true frequency of granulomatous infiltration in the disease and assist in understanding the pathogenesis of the reaction.

Symptoms and Signs

The syndrome usually develops within 2 months after drug introduction, more often in 3 weeks to 3 months of the introduction of the drug, or earlier if constituting readministration. Fever, often high (38°–40 °C), which is the most common symptom (seen in 90–100% of cases), and rash (87% of cases) are the first signs, especially when related to antiepileptic drugs. The cutaneous eruption consists of a morbilliform rash, which is indistinguishable from the rash of other less severe reactions (Fig. 26.12b, c).

The face, upper trunk, and upper extremities are initially affected, with subsequent progression to the lower extremities occurring in about 90% of cases, which later spreads to the legs and the development of erythrodermic rash.

The maculopapular eruption later becomes infiltrated with edematous follicular accentuation. Swelling of the face, with marked periorbital involvement, is a warning for the diagnosis, occurring in about 25% of patients, and can be so intense that the patient becomes disfigured.

Fig. 26.12 Clinical and histopathologic findings in a patient with DRESS caused by dapsone during leprosy treatment. (**a**) Epidermis showing spongiosis, apoptotic keratinocytes, exocytosis of lymphocytes, and inflammatory infiltrate in the superficial dermis (hematoxylin–eosin, ×200 OM); (**b, c**) Exanthema in DRESS in Caucasian woman
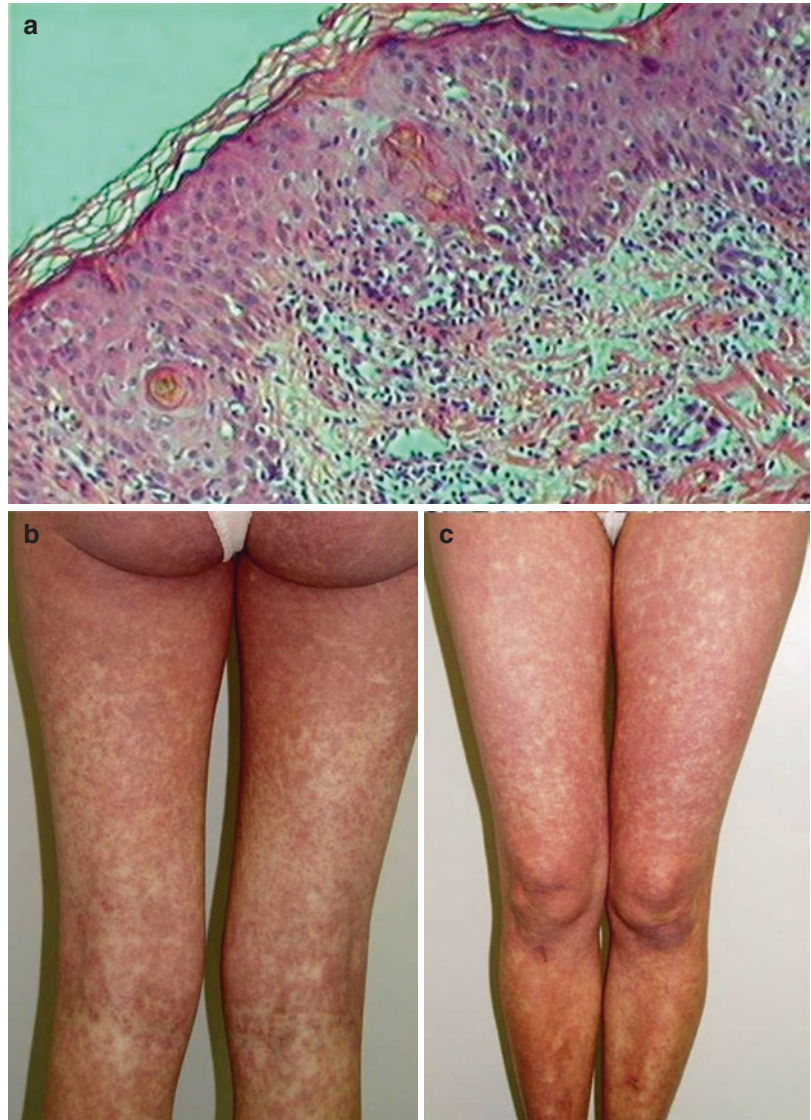
Vesicles may arise, and fine bubbles caused by edema of the dermis can be present. No necrosis of the epidermis such as TEN occurs, except in rare cases of overlapping DRESS/DIHS and TEN. Small sterile perifollicular pustules and nonfollicular pustules may appear, which are different from acute generalized exanthematous pustulosis and do not predominate on the main ridges of the skin. Often atypical targets may arise. Over time the rash becomes purplish, with sharp definition on lower limbs and the resolution of scaling Another form of presentation is a picture of exfoliative dermatitis, which may be associated with mucosal involvement, such as cheilitis, erosions, pharyngitis, and enanthematous enlarged tonsils.

Bilateral edema and infiltration of the salivary glands with xerostomia has been frequently reported.

Lymphadenopathy is common (70–75% of cases), limited to the lymph nodes or generalized, and painful, gradually resolving with the withdrawal of the drug. The lymph nodes may reveal two distinct types of involvement: a benign pattern of lymphoid hyperplasia with maintenance of normal lymph node architecture, and another

standard pseudolymphomatous aspect, with obliteration of normal architecture by a polymorphous infiltrate composed of atypical cells, plasma cells, histiocytes, and eosinophils, with areas of necrosis, edema, and mitotic figures but no Reed–Sternberg cells or capsular invasion. This histopathologic pattern can simulate a malignant lymphoma.

Various hematologic abnormalities are observed, which consist of marked leukocytosis, eosinophilia (30% of cases), and atypical lymphocytes similar to mononucleosis. These findings guide the diagnosis toward DRESS, but can sometimes be difficult to distinguish from viral infections such as infection by EBV or hematologic diseases. Lymphopenia, leukopenia, or leukocytosis usually precedes it, although they often are not detected because they occur several days before establishment of the clinical syndrome. Leukocytosis may be high, up to 50,000 leukocytes/mm^3, and eosinophilia reaches values higher than 20,000/mm^3. The eosinophilia may determine the involvement of internal organs with pulmonary infiltrates. In general, eosinophilia may be observed about 1–2 weeks after the onset of the syndrome, or may even occur after the increase in liver enzymes has normalized.

Hemophagocytic syndrome (HPS) can rarely be observed in the course of DRESS/DIHS. HPS is associated with and triggered by various conditions, including viral infections, particularly EBV, malignant tumors, or autoimmune diseases. When involved with the course of DRESS/DIHS, HPS usually occurs 2 weeks after the onset of drug eruption. There is a decrease in white blood cells and platelets that are detected simultaneously with elevation of lactate dehydrogenase (LDH). Bone marrow aspirate reveals hemophagocytosis in an increased number of macrophages.

Multiorgan involvement may include a wide variety of organs and systems with myocarditis/myositis, pericarditis, interstitial nephritis (11% of cases), necrotizing granulomatous vasculitis in kidney, brain involvement (encephalitis or meningitis), colitis, and thyroiditis. This potentially fatal visceral involvement form may be symptomatic or not, and begins 1–2 weeks after the onset of rash. We observed a patient who

developed acute pancreatitis that evolved into a lethal course.

There are reports of shock and respiratory distress syndrome with hypotension, pyrexia, hepatitis, and renal failure related to a hydantoin reaction.

Arthritis or arthralgia may occur in the context of this syndrome, including myositis.

Liver involvement is the most common visceral manifestation (50–60% of patients) after lymphadenopathy. Hepatomegaly may constitute a finding on physical examination. Hepatitis with isolated elevation of liver transaminases is common (51% of cases), usually anicteric, but liver failure is a leading contributory factor to mortality. Liver biopsy shows central lobular necrosis and dense inflammatory infiltrate of lymphocytes and eosinophils or granulomas. The reaction is accompanied by cholestasis and hepatocyte necrosis. In more severe cases, widespread or focal hepatic necrosis may be present. The presence of an active coinfection with hepatitis viruses B and/or C often determines deterioration in liver function and prolonged liver dysfunction.

There are few cases reported in the literature of DRESS/DIHS with severe acute hepatitis (defined by the presence of alanine aminotransferase (ALT) to more than 10× upper limit of normal and/or acute liver failure, such as coagulopathy and encephalopathy), mostly observed in women between the second and fourth decade of life, especially in relation to the use of sulfasalazine. About 15% result in death or liver transplantation, and the course of the disease is apparently unchanged by the use of immunosuppressants. The rapid recognition of the syndrome and prompt withdrawal of the drug can limit the liver damage, although this may be possibly even worse for several weeks and take months to resolve.

Renal involvement occurs in about 11% of cases, being particularly evident in cases arising from the use of allopurinol, whereby there was an increase in serum creatinine and urea and decreased creatinine clearance. In urine tests, increased content of eosinophils can be observed.

Although pulmonary involvement is rarely reported in DRESS/DIHS, interstitial pneumonia

with eosinophilia is often observed among patients whose syndrome was triggered by minocycline. Possibly the cases with lower intensity of pulmonary manifestations are less reported, leading to a bias in the published literature. Pulmonary complications include acute interstitial pneumonitis, lymphocytic interstitial pneumonia, and adult respiratory distress syndrome (ARDS).

Myocarditis may develop at the beginning of the syndrome or up to 40 days after establishment. Symptoms include heart failure, chest pain, sudden tachycardia, dyspnea, and hypotension in early DRESS/DIHS, but some patients are asymptomatic. The echocardiogram shows a reduction in ejection fraction, chest X-ray demonstrates cardiomegaly, and the electrocardiogram shows nonspecific changes in the ST-T segment. There is an increase in enzymes such as CPK and CK-MB, but no apparent changes in levels of troponin-1.

Neurologic complications include meningitis and encephalitis. Meningoencephalitis occurs about 2–4 weeks after initiation of drug reaction, and may lead to coma, seizures, headaches, disorders of speech, and paresis and paralysis of the cranial nerve.

Gastrointestinal bleeding may be an abrupt complication caused by ulcers derived from CMV. Endoscopic examination reveals arterial bleeding from punched-out gastric ulcerations.

Kennebeck compiled the frequency of clinical manifestations and laboratory data of the anticonvulsant hypersensitivity syndrome: fever (90–100%), cutaneous eruption (87–90%), lymphadenopathy (70%), hepatitis (50–60%), hematologic abnormalities (23–50%), periorbital and orofacial edema (25%), myalgia and arthritis (20%), nephritis (11%), pharyngitis (10%), and pulmonary manifestation (9%).

The visceral involvement in acute DRESS/DIHS until resolution of clinical disease is, therefore, extensive and varied, some of these events being closely related to HHV reactivation: enterocolitis and intestinal bleeding, hemophagocytic syndrome (HPS), hepatitis, limbic encephalitis, myocarditis, nephritis, mumps, pneumonia, pleurisy, and the syndrome of inappropriate antidiuretic hormone (SIADH).

The exclusion of other serious infections, particularly bacteremia, neoplastic diseases (lymphoma, leukemia, hypereosinophilic syndrome, paraneoplastic syndrome), and autoimmune or connective tissue conditions (adult-onset Still's disease, lupus erythematosus, vasculitis) is necessary for an accurate diagnosis of DRESS/DIHS.

Complications are rare and include limbic encephalitis, thyroid disease, renal failure, splenic rupture, eosinophilic colitis, eosinophilic esophagitis, enterocolitis, and fatal CMV.

The mortality rate can reach 20%, especially in cases related to advanced age, renal impairment, jaundice, and hepatitis with reactivation of CMV. By contrast, cases where there is a reactivation of EBV seem to have a less severe course, but are more likely to later (usually after several years) develop autoimmune diseases such as diabetes mellitus type 1 and autoimmune hypothyroidism.

Several authors have reported the occurrence of autoimmune diseases and/or the production of autoantibodies after the resolution of DRESS/DIHS, in a period ranging from several months or years after the resolution of the syndrome, and some are similar to those seen after bone marrow transplant. The related conditions include diabetes mellitus type 1, lupus erythematosus, Hashimoto's thyroiditis, enteropathy, sclerodermiform lesions, GVHD, and bullous pemphigoid.

Diagnostic Criteria

The diagnosis is difficult since there are incomplete or less characteristic clinical features, for example, hepatitis without rash, or merely pulmonary infiltrate with eosinophilia. Bocquet, Bagot, and Roujeau were the first authors who proposed criteria for DRESS diagnosis. According to these authors the diagnosis is established if there are at least three criteria present:

1. Drug rash
2. Hematologic abnormalities
   (a) Eosinophilia >1,500/mm^3
   (b) Presence of atypical lymphocytes

3. Systemic involvement (adenopathy (>2 cm in diameter) or hepatitis (transaminase elevation at least twice the normal values) or interstitial nephritis, pneumonitis, or carditis.

There is still no international consensus on the best criteria for the definition of DRESS/DIHS diagnosis. Bocquet et al. and Southeimer and Houpt have proposed different definitions and nosology for DRESS/DIHS in order to clarify clinical and pathologic characteristics of this syndrome.

The Japanese study group for severe cutaneous adverse reactions to drugs (SCAR-J) has adopted other criteria, as presented on Chart 26.4.

However, the universal adoption of these criteria may be impaired, because one of the criteria is viral replication during the course of infection, and some tests, such as measurement of IgG titer anti-HHV-6, are not yet routinely available in all hospitals or laboratories.

In our view, the criteria adopted by the European group RegiSCAR, published by Kardaun et al. in 2007, is the best to meet the needs in the diagnosis of DRESS/DIHS. Here the use of a system score for the diagnosis of DRESS/DIHS was suggested, based on the presence of symptoms and clinical and laboratory signs, as displayed in Table 26.1.

Complementary Tests During Follow-Up of Patients with DRESS/DIHS

Given the suspicion of the syndrome relevant examinations should be performed, keeping in mind that this syndrome has evolutionary behavior. The initial tests are oriented to verify the data and research into hematological visceral involvement, as proposed by Descamps et al. At admission: complete blood count, ALT, aspartate aminotransferase (AST), total bilirubin, γ-glutamyl transferase, alkaline phosphatase, sodium, potassium, creatinine and creatinine clearance, 24-h urine protein and urinary eosinophil count, CPK, LDH, ferritin, triglycerides, calcium and parathyroid hormone, blood glucose, prothrombin time and activated partial

Chart 26.4 Diagnostic criteria for DRESS/DIHS proposed by Japanese group

1. Maculopapular rash developing >3 weeks after starting therapy with a limited number of drugs
2. Persistent clinical findings after drug withdrawal
3. Fever (>38 °C)
4. Hepatic abnormalities (glutamic pyruvic transaminase >100 U/l)[a]
5. Leukocyte abnormalities (at least one present)
(a) Leukocytosis (>11,000/mm^3)
(b) Atypical lymphocytosis (>5%)
(c) Eosinophilia (>1,500/mm^3)
6. HHV-6 reactivation[b]

The diagnosis is confirmed by the presence of the seven criteria (typical DIHS) or of the first five criteria (atypical DIHS)

[a]This can be replaced by other organ involvement such as renal involvement

[b]Reactivation is detected from the second to third week after symptom onset, through IgG anti-HHV-6 titer elevation

thromboplastin time, lipase, protein electrophoresis, C-reactive protein, quantitative PCR for HHV-6, -7, EBV, and CMV, blood culture, and antinuclear factor.

Follow-up (two times per week): complete blood count, ALT, AST, creatinine, LDH, and other laboratory tests according to changes found on admission tests. Evolutive follow-up: quantitative PCR for HHV-6, -7, EBV, and CMV, complete blood count, ALT, AST, alkaline phosphatase, creatinine, LDH, ferritin, and triglycerides.

Treatment

The early recognition of ADRs and withdrawal of the offending drug is the most important and essential steps toward clinical improvement. Empiric treatment with antibiotics or anti-inflammatory drugs should not be administered during the acute disease, since they may confuse or worsen the clinical picture of patients because of an unexplained cross-reactivity between drugs.

Prognosis is generally worse in the elderly while the recovery is usually faster and usually complete in children.

For many years, the treatment of DRESS has been based on the use of systemic corticoste-

Table 26.1 Scoring system for classifying DIHS/DRESS cases as definite, probable, possible, or no case (Adopted by RegiSCAR (Register of Severe Cutaneous Adverse Reactions) [44])

Score	−1	0	1	2	Max	Min
Fever ≥38.5 °C	No/U	Yes			−1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia:		No/ U			0	2
Eosinophils			0.7–1.499 × 210^9 l^{-1}	≥1.5 × 10^9 l^{-1}		
Eosinophils, IF leukocytes <4.0 × 10^9 l^{-1}			10–19.9%	≥20%		
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement					−2	2
Skin rash extent (% body surface area)		No/U	>50%			
Skin rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	No/U				
Organ involvement*:					0	2
Liver		No/U	Yes			
Kidney		No/U	Yes			
Muscle/heart		No/U	Yes			
Pancreas		No/U	Yes			
Other organ		No/U	Yes			
Resolution ≥15 days	No/U	Yes			−1	0
Evaluation of other potential causes:						
Antinuclear antibody (FAN)						
Blood culture						
Serology HAV/HBV/HCV						
Chlamydia/mycoplasma						
*If none positive and ≥3 of above negative			Yes		0	1
Total score					−4	9

U unknown/unclassifiable, *HAV* hepatitis A virus, *HBV* hepatitis B virus, *HCV* hepatitis C virus

After exclusion of other explanations: *1* one organ, *2* two or more organs. Final score <2, no case; final score 2–3, possible case; final score 4–5, probable case; final score >5, definite case

*Organ involvement

roids (dose equal to or greater than 1–1.5 mg/kg/day of prednisone or equivalent) with marked improvement of symptoms and laboratory parameters only several days after the start of treatment. Systemic corticosteroids should have their dose reduced, after clinical and laboratory control of the disease, slowly over 6–8 weeks to prevent recurrence of the symptoms of disease. Abrupt deterioration of various symptoms is observed when the withdrawal is accidental or by rapid reduction of the dose of corticosteroids. Shiohara et al. recommend that all patients should be hospitalized even when the initial presentation is mild.

If symptoms worsen despite the use of oral corticosteroids, other options used in case series are the use of pulsed methylprednisolone (30 mg/kg intravenously for 3 days), intravenous immunoglobulin (IVIG), and plasmapheresis, or a combination of these therapies. It should be remembered that the immunosuppressive therapies may increase the risk of infectious complications and sepsis. Mild cases can recover simply by drug withdrawal and supportive treatment after a few weeks, even without the use of corticosteroids. However, even in mild cases, the monitoring of liver function tests should be conducted and appropriate tests ordered to rule out the involvement of other organs such as lungs, thyroid, and heart.

Special attention should be given to possible reactivation of CMV, especially in patients with severe DRESS/DIHS. Physicians should also pay attention to a proper balance between the needs of corticosteroids for relief of symptoms and

clinical signs and their possible negative influence on viral load.

High doses of IVIG have two immunologic effects: (i) it compensates for the decrease in concentration of immunoglobulins in patient's blood and the defects in immune protection against HHV-6; and (ii) high doses of IVIG have an anti-inflammatory effect that can regulate immune responses, as seen in the treatment of autoimmune diseases.

The French Society of Dermatology published the results of a consensus of experts on the therapeutic management of DRESS/DIHS regarding drug reactions:

- Absence of signs of gravity: corticosteroids (potent or very potent), emollients, H1-antihistamines
- Presence of signs of severity (transaminases >5 times normal renal organic, pneumonia, hemophagocytosis, cardiac, etc.): corticosteroids equivalent to 1 mg/kg per day of prednisone, multidisciplinary evaluation
- Life-threatening signs (hemophagocytosis with bone marrow failure, encephalitis, severe hepatitis, renal failure, respiratory failure): steroids generally associated with IVIG at a dose of 2 g/kg over 5 days. The IVIG should not be proposed without associated steroids. These treatments to be conducted through multidisciplinary evaluation
- Presence of signs of gravity with confirmation of a major viral reactivation: Combining steroids and antiviral (ganciclovir) and/or IVIG

Kano et al. reported the occurrence of herpes zoster in 3 of 28 patients with DRESS/DIHS within 6 months after the onset of DRESS/DIHS; all three patients had been given systemic corticosteroids and the ADR was triggered by anticonvulsants. The authors suggested that the administration of systemic corticosteroid for the treatment of DRESS/DIHS may have contributed to the increased risk of herpes zoster. Indeed, herpes zoster was not detected in patients with DIHS/DRESS who were treated with only supportive care. Presumably, the altered underlying immunologic pathomechanism of DIHS/DRESS caused by the systemic corticosteroid might have played an important role in the onset of herpes zoster. It has been shown that DIHS/DRESS is a manifestation of newly observed immune reconstitution syndrome (IRS), and herpes zoster is observed as the most common manifestation of IRS after highly active antiretroviral therapy for AIDS. Relevant clues related to DRESS syndrome include:

- DRESS/DIHS is an ADR caused by an apparent group of drugs, and one-third of cases are related to anticonvulsants, in addition to sulfonamides and allopurinol, which can cause 10–20% mortality.
- The syndrome is characterized by a latency period ranging between 3 weeks and 3 months after the introduction of the offending drug, and its course is marked by apparent sequential reactivation of HHV and subsequent development of autoimmune diseases, providing an opportunity to establish a connection between viral infections and the emergence of autoimmune diseases.
- In early DRESS/DIHS hypogammaglobulinemia and reduced peripheral B cells are found, and CD4+ CD25+ FoxP3+ (regulatory T cells) levels are high at the beginning of the syndrome, regardless of whether or not patients are treated with corticosteroids. This clonal expansion of regulatory T cells appears to prevent activation of antiviral T cells in an appropriate manner and sequential reactivation of virus is presented in the syndrome. These regulatory T cells have the phenotype CCR4+ and CLA+, which address the skin. In the last stage of the syndrome's activity, phenotype of cytotoxic T cells becomes prominent and CD4+ lymphocytes are intensely diminished. These cells are depleted over time, suffering apoptosis and becoming reduced after the resolution of the syndrome, which could be a predisposing factor for the development of autoimmunity.

Acute Generalized Exanthematous Pustulosis [45]

AGEP is a clinical entity that appears in the intertriginous areas or on the face as a diffuse erythema (scarlatiniform) with acute presentation. Patients

Fig. 26.13 AGEP. Several pinhead sterile pustules over erythematous skin
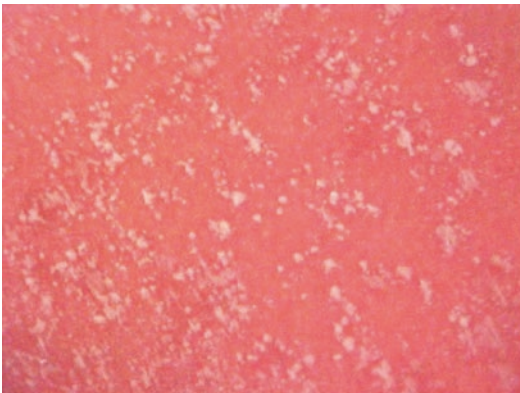
Fig. 26.14 AGEP. Detail of confluent pinhead pustules

report pruritus or local burning sensation. After this appearance, the erythema is replaced by hundreds of nonfollicular sterile small pustules (<5 mm in diameter) (Figs. 26.13 and 26.14). These pustules may sometimes converge and

mimic Nikolsky's sign, leading to misdiagnosis as TEN. Intense edema of the face may occur, with purpuric lesions mainly on the legs and the onset of lesions similar to EM of the legs.

There may be mucous involvement in about 20% of the patients, although it is usually mild and self-limited, occurring in just one location. The cutaneous symptoms are almost always accompanied by fever of >38 °C. Frequently there is leukocytosis in the blood count, and eosinophilia may also occur in one-third of the patients.

Usually this eruption regresses within 4–10 days after withdrawal of the drug and in typical cases leaves a lamellar or punctiform desquamation. Disease prognosis worsens when there is hyperthermia or infection of the lesions, and when it affects elderly individuals, who should be hospitalized.

The drugs described as a cause of AGEP are most frequently β-lactams (penicillin, cephalosporins), macrolides (azithromycin, erythromycin), cyclines (doxycycline), sulfonamides (trimethoprim, sulfasalazine), chloramphenicol, isoniazid, streptomycin, vancomycin, quinolones (ciprofloxacin, norfloxacin), itraconazole, terbinafine, allopurinol, carbamazepine, phenytoin, diltiazem, nifedipine, chromium picolinate, diclofenac, enalapril, disulfiram, furosemide, hydroxychloroquine, paracetamol, mercury, thalidomide, protease inhibitors, and bamifylline.

Sidoroff and et al. proposed some characteristics that might aid in the differentiation between pustular psoriasis and AGEP. In the latter, a history of psoriasis is rare, the lesions are most frequent in the cutaneous folds, the duration of the fever and the pustules is short, and there is usually a history of recent exposure to the drug; arthritis is rare.

Histopathology may show subcorneal and/or intraepidermal spongiform pustules, edema of the papillary dermis, vasculitis, exocytosis of eosinophils, and focal necrosis of keratinocytes (Fig. 26.15). On the other hand, in pustular psoriasis a history of psoriasis is common, the involvement is generalized, the duration of the fever and the pustules is longer, history of drug exposure is less frequent, arthritis occurs in about 30% of the patients, and histopathologic
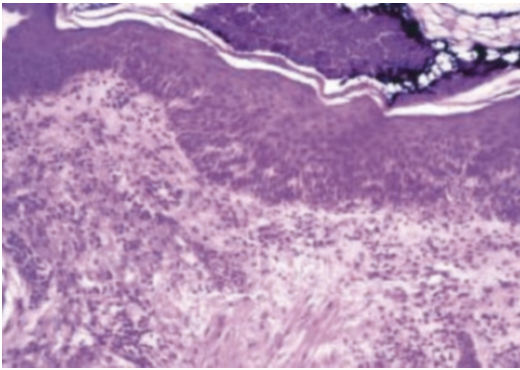
Fig. 26.15 AGEP histopathology. Subcorneal pustule without psoriasiform epidermal hyperplasia

examination shows subcorneal and/or intraepidermal pustules, papillomatosis, and acanthosis of the epidermis.

Skin tests for late-phase reactions may be useful tools for identifying the etiologic agent of AGEP when the systemic readministration is potentially dangerous. Approximately 50% of the cases of AGEP present positive contact tests for the suspect drug, usually reproducing the lesion in both a clinical and histologic form.

Recently, Britschgi and colleagues demonstrated high expression of IL-8 in these patients. It is known that IL-8 is a chemokine with potent activity in the recruitment of neutrophils, which is produced by the keratinocytes and mononuclear cells of the cutaneous inflammatory infiltration. These authors concluded that AGEP might be the expression of a reaction whereby a cell bound to the drug triggers a drug-specific CD4$^+$ and CD8$^+$ immune response, which results in high expression of IL-8 (Type VId in the Pichler classification).

Drug-Induced Serum Sickness [45]

In 1905, Von Piquet and Shick described serum sickness in children treated with horse serum containing diphtheria antitoxin. More recently serum sickness has been observed in patients treated with horse antithymocyte globulin or vaccines of rabbit antihuman diploid cells. This constitutes a type III hypersensitivity reaction, mediated by immunocomplexes deposited on the walls of the vessels, activation of the complement, and recruitment of granulocytes.

It presents particular cutaneous manifestations: typically there is erythema in the lateral portion of the fingers and toes that precedes a more disseminated eruption (occurring in 90% of cases), which frequently is morbilliform (two-thirds of the patients) and sometimes urticariform. The presence of urticaria, leukocytoclastic vasculitis, and multiform erythema is rarely observed. In half of the cases there is visceral involvement [1]. The following clinical findings are common: fever, cutaneous eruption, constitutional symptoms, arthritis, and arthralgia.

The disease begins about 8–14 days after the initial exposure to the foreign protein. The drugs related with this type of manifestation are the heterologous sera and vaccines. Serum sickness-like reactions can also be caused by penicillin, cephalosporin, minocycline, propranolol, streptokinase, and nonhormonal anti-inflammatories. There are no data on the prevalence of this disease in Brazil, although reports of cases of this disease are not infrequent in the medical literature.

Fractions C3 and C4 of the complement are strongly decreased in serum sickness while they are usually normal in serum sickness-like reactions.

Treatment of the disease constitutes withdrawal of the drug allied to the use of systemic corticosteroids, in addition to antihistamines for symptomatic relief of pruritus when present. Careful observation of the clinical course of the patient's systemic involvement is imperative.

Drug-Induced Vasculitis [45, 46]

Several medications can induce a cutaneous vasculitis-type response, the histopathologic definition of which is the presence of inflammation and necrosis in the wall of the cutaneous blood vessels. Clinically it presents as tangible purpura or maculopapular purpuric eruption. This disease can also occur in the form of hemorrhagic blisters, urticaria, ulceration, nodules, Raynaud's disease, and digital necrosis. The same vasculitis

process can involve internal organs, such as the kidneys, liver, gastrointestinal tract, or the central nervous system, and any area of the tegument, including the mucous membranes and the palmar and plantar regions.

The disease develops about 7–21 days after initiating the drug; however there can be a longer time interval, and any medication instituted within the 2 months prior to the presentation should be considered suspect. Given the absence of confirmatory tests for this entity, one should value anamnesis and the correlation with drug exposure, which in general occurs 1–3 weeks before onset of the cutaneous picture. However, the exposure can have occurred in periods as disparate as 2 days to 9 years. Withdrawal of the drug leads to a rapid resolution of the picture, and systemic corticosteroids can benefit some patients. The process is usually solved without sequels.

The clinical, epidemic, and pathologic characteristics of drug-induced vasculitis have been little reported in the medical literature, since there is no consensus in the definition of this disease, with various revisions using different criteria for inclusion of cases. Vasculitis attributed to exposure to medicines is rare, but seemingly account for about 10–20% of dermal vasculitis cases. It is difficult to quantify the frequency with which drug-induced vasculitis is strictly cutaneous.

Clinical experience suggests that most of the cases are confined to the skin and have a self-limited course, although it can be associated with varied degrees of systemic symptoms including arthralgia, indisposition, and fever. Visceral involvement is well described and pathologically heterogeneous. Glomerulonephritis and interstitial renal disease, varied degrees of hepatocellular damage, and formation of granulomas in the liver have been described, besides involvement of the heart, lungs, and central nervous system. Furthermore, there are rare cases of drug-induced vasculitis with renal and hepatic involvement in the absence of cutaneous disease.

The drugs most frequently referred to in the literature, in the form of case reports or series studies, as causative of vasculitis are propylthiouracil, hydralazine, granulocyte colony-stimulating factor (G-CSF), cefaclor, minocycline, allopurinol, D-penicillamine, phenytoin, isotretinoin, and methotrexate.

As many of the cases of drug-induced vasculitis are not reported in the literature, other drugs are also possible important causative agents of this reaction type. Other drugs have been reported less often as causal agents of vasculitis: several antibiotics, etretinate, didanosine, zidovudine, acebutolol, atenolol, sotalol, propranolol, chlorothiazide, furosemide, diltiazem, nifedipine, methyldopa, captopril, enalapril, lisinopril, losartan, procainamide, quinidine, antithyroid medications, painkillers and antipyretics, levamisole, tamoxifen, arabinoside C, interferon, interleukin-2, sulfasalazine, etanercept, gold, carbamazepine, antidepressants, zafirlukast, chromalin, cimetidine, ranitidine, L-tryptophan, radiocontrast, streptokinase, heparin, coumarin, chlorpromazine, metformin, pimagedine, and diphenhydramine.

Drugs that induce vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) include hydralazine, propylthiouracil, minocycline, and anti-TNFα biological agents.

About 20% of the patients who use propylthiouracil develop ANCA, a fact that is related to a higher risk of glomerulonephritis. A particularly relevant form among the drug-induced vasculites is propylthiouracil hypersensitivity vasculitis. There are cases with other antithyroid compounds, such as methimazole, thiamazole/methylthiouracil, and carbimazole, which, similarly to propylthiouracil, contain a thioamide group and cause allergic cross-reactions. Although uncommon, nowadays a larger number of case reports of this entity are observed, suggesting that cases were previously not reported or were included among other nosologic entities, since propylthiouracil is a drug classically dedicated to the treatment of hyperthyroidism.

The clinical symptoms and signs begin after initiating propylthiouracil. Although the duration of drug use is extremely variable, from 1 week to 13 years, it appears under a classic tetrad of symptoms that include fever, sore throat, arthralgia and cutaneous eruption; there can also be myalgia, fatigue, weight loss, conjunctivitis, rhinitis, and hemoptysis.

The disease course is that of a systemic vasculitis. There can be a lupus-like syndrome, Wegener-like granulomatosis, or nodular-like polyarthritis with multiple involvement of organs, such as kidneys, joints, lungs, and others associated with cutaneous lesions. The cutaneous lesions usually consist of plaques or acral purpuric nodules arranged in a livedoid pattern, with a preference for the extremities (Fig. 26.16), face, breasts, and characteristically the lobes and helices of the ears, mimicking the leprosy type reaction of Lucio's phenomenon. Hemorrhagic blisters appear on these lesions that progress to central necrosis of the skin, which can be so extensive that it simulates the clinical presentation of purpura fulminans observed in septic infectious states with disseminated intravascular coagulation.

Laboratory tests reveal anemia, leukopenia, and platelet depletion in the blood count; increased erythrocyte sedimentation rate, urea, creatinine, transaminases, and bilirubin; hypoalbuminemia; alterations in the coagulation time, prothrombin time, and partial activated thromboplastin time; and immunological abnormalities such as positive ANCA, rheumatoid factor, and hypergammaglobulinemia can be found. Positivity can also be present in anti-SSA, anti-double-stranded DNA, anticardiolipin, anti-smooth muscle antibodies, antimitochondrial, parietal, and antiadrenergic antibodies, besides hypocomplementemia, cryoglobulinemia, and elevation of C-reactive protein.

Histopathologic study demonstrates a leukocytoclastic vasculitis of the superficial and profound vessels of the dermis. The finding of immunocomplexes deposited in the vascular wall is uncommon, such that some authors have named them pauci-immune ANCA-positive vasculitis. Most of the patients recover completely following withdrawal of propylthiouracil, although some develop impairment of the kidneys or other internal organs, or skin, requiring high doses of prednisone for several months.

The dermatologic findings in patients with drug-induced vasculitis associated with ANCA include plaques and purpuric acral nodules, which appear more commonly on the extremities, face, breasts, and ears. In addition, the patients report the same signs and symptoms as found in other small-vessel vasculites associated with ANCA (Wegener's granulomatosis, Churg–Strauss syndrome), including glomerulonephritis, pulmonary hemorrhage, and digital gangrene.

Besides withdrawal of the offending drug, it is generally necessary to use corticosteroids in high doses or in pulse therapy, plasmapheresis, and immunosuppressants for several months. The mortality rate is approximately 10%.

Fig. 26.16 Retiform purpura in drug-induced ANCA-positive vasculitis caused by propylthiouracil

Anticoagulant-Induced Skin Necrosis [45]

This is a rare and severe adverse effect from treatment with warfarin (anti-vitamin K agents), occurring with cutaneous necrosis secondary to occlusive thrombosis in the vessels of the skin and subcutaneous cellular tissue. It usually presents 3–5 days after use of the drug, as painful

Fig. 26.17 Anticoagulant-induced skin necrosis caused by warfarin. Note thrombosis of femoral vessels in histopathologic examination

erythematous plaques that course to necrosis (Fig. 26.17), with hemorrhagic blisters or necrotic scars in the areas rich in subcutaneous tissue, such as buttocks, breasts, and hip. The risk of this disease increases in patients who are female, obese, and users of high doses of the medication [1]. The necrotic tissue requires debridement and grafts. This type of reaction has also been described with the use of heparin.

Moderate or Mild Cutaneous Adverse Drug Reactions (CADRs) or Uncomplicated CADRs

This kind of ADR is represented by several conditions related to drug exposure, which do not represent life-threatening conditions to the patients except discomfort. There is no severe temporary or permanent remaining lesions or long-term internal organ sequelae and, in most of cases, no mortality or severe impact on patients' health. In contrast to severe ADRs, in the clinical setting of uncomplicated CADRs admission to the intensive care or burn unit is usually not necessary for the majority of patients.

For this reason, the physician must be able to identify the signs and symptoms that indicate severe CADR [47]. In particular, dermatologists must pay attention to identifying these reactions, since the skin is among the most common organs or systems of clinical manifestation of ADRs and concurs with at least 15% of ADRs [47].

The most common forms of CADRs are urticarial and exanthematous eruptions, which together constitute 90–95% of all CARDs [47]. These two types carry few to no long-term consequences [47]. The severe ADRs (SADRs), described earlier in this chapter, probably represent around 2% of all ADRs [47]. SADRs often are associated with high levels of morbidity and mortality, and therefore a prompt recognition of the reaction, withdrawal of all possible offending agents, and appropriate triage, hospital admittance, workup, and specific treatment are critical [47].
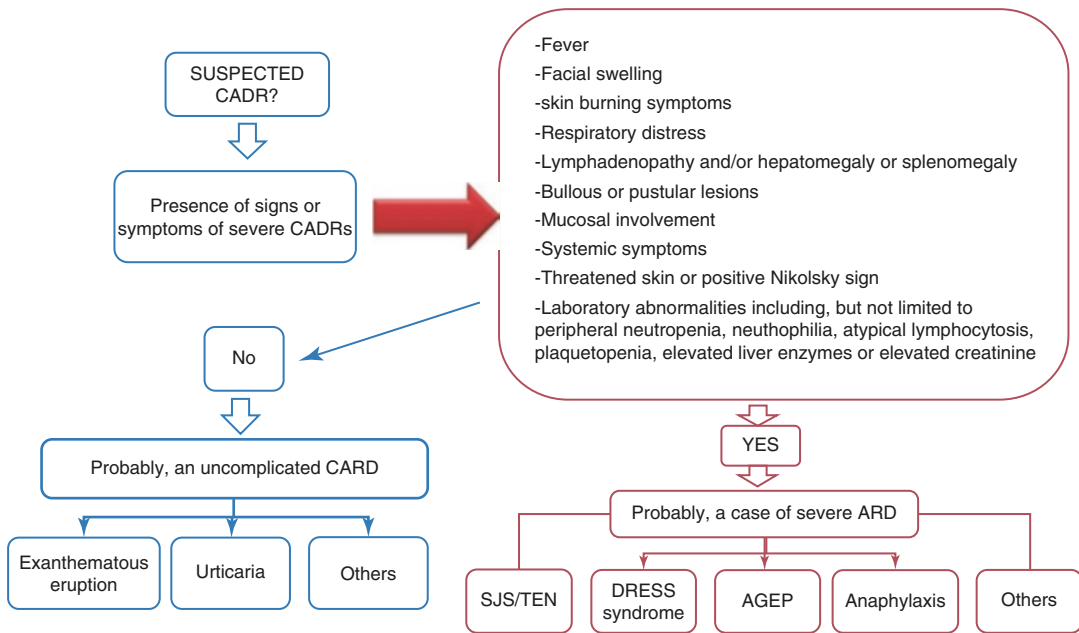
Fig. 26.18 Algorithm for evaluation of patients with ADR based on signs and symptoms indicating a severe or an uncomplicated ADR

Regarding studies of severe versus uncomplicated ADRs, Swanson and Colven [47] proposed a staged patient evaluation as shown in Fig. 26.17. Signs and symptoms severe ADR are listed in Fig. 26.18, and in this clinical scenario the physician should have a low threshold to admit the patient to hospital, perform a complete workup including evaluation of other medical specialties, withdraw suspected medications, and initiate adequate therapy when indicated [47].

Another relevant aspect in recognizing the type of ADR is the time from medication introduction to the onset of a cutaneous reaction, since this is related to the subtype of ADR, as proposed in Fig. 26.19 [47]. Often patients have been exposed to several medications in the same period, and creating a "drug list" that details the dates of all medications taken is helpful in narrowing down the most probable culprits [47].

Physicians should pay attention to prodromal symptoms (skin pain, fever, malaise, throat pain or discomfort, arthralgia, etc.) that can to precede the cutaneous eruption, and associated internal symptoms (abdominal pain, ocular discomfort, dysuria, respiratory distress, etc.), and proceed to complete physical examination including full skin examination of groin, genitalia, eyes, oropharynx, thorax auscultation, abdomen, and lymph node palpation [47].

The physician needs remember that several risk factors for the development of more severe cutaneous ADRs have been identified, including female gender, older age, viral infections (herpesvirus family or HIV), genetic susceptibility (specific single-nucleotide polymorphisms in the HLA region), iatrogenic immunosuppression, underlying immune-mediated diseases, and cancer [48].

Exanthematous Drug Eruptions [48, 49]

Exanthematous or maculopapular drug eruptions, sometimes inappropriately designated "drug rashes" or "drug eruptions" by some generalists, are the most common ADRs in the skin. The eruption usually occurs between 4 and 14 days after the initiation of a new medication or chemical substance, although it can develop sooner,

Acute urticaria Minutes to few days						
AGEP > 4 days						
Warfarin-skin necrosis 4-7 days						
Exanthema 4-14 days						
SJS/TEN 7-21 days						
DRESS 14-60 days						
ANCA+ vasculitis moths to years						
Time since drug introduction	1 day	5 days	10 days	15 days	60 days	Months to years
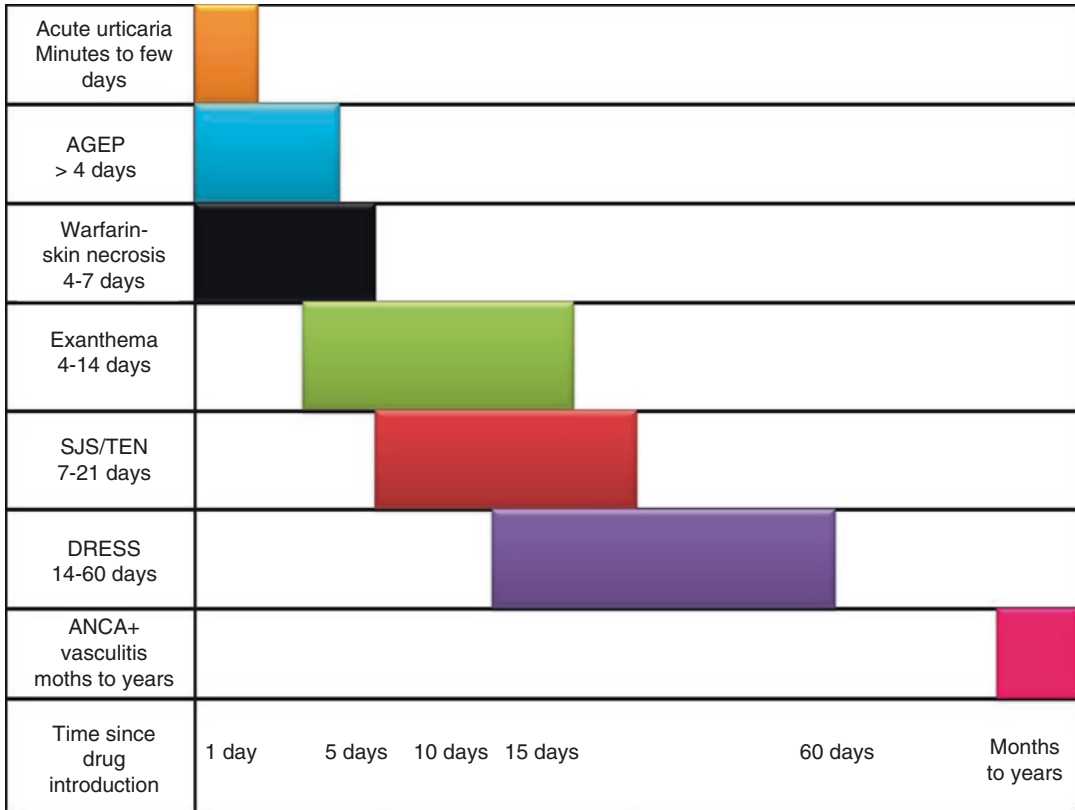
Fig. 26.19 Approximate timing of drug eruptions after the onset of drug introduction

especially in case of a new exposition to the same or parent drug. Uncomplicated exanthematous drug reactions usually resolve in a few days when the causative drug is stopped.

Exanthematous eruptions generally are composed of erythematous macules and/or papules and more rarely by vesicles or pustules, usually with a pattern of symmetric distribution on skin. The eruption often begins on the trunk followed by centrifugal dissemination to the proximal limbs. Skin lesions progressively become confluent and may cover large areas of the body (Fig. 26.20). Pruritus and/or low-grade fever are often associated with the exanthema. In some patients the exanthema may progress to erythroderma or more severe reactions such as SJS/TEN or DRESS syndrome after some days or weeks.

Under histopathology examination this type of ADR demonstrates interface dermatitis with vacuolar changes in keratinocytes at the basal

Fig. 26.20 Morbilliform drug-induced exanthema

layer of the epidermis, and upper dermal mononuclear cells infiltrate with some eosinophils. The pathogenesis involves the overexpression of several cytokines of Th2 pattern, such as IL-5 and IL-13, causing epidermal damage by

molecules of perforin, granzyme B, and peripheral blood eosinophilia (a type IVb delayed cell-mediated immune mechanism, as proposed by Werner Pichler).

Uncomplicated exanthematous drug eruptions can occur with almost any medication, but the following drugs have higher risks (more than 3% of patients): allopurinol, aminopenicillins, cephalosporins, antiepileptic drugs, and antibacterial sulfonamides. Viral infections may increase the incidence of morbilliform drug eruptions, as seen in the setting of mononucleosis infection under treatment with ampicillin, or in severe exanthema with internal damage as in DRESS syndrome related to the HHV family (EBV, cytomegalovirus, HHV-6 and -7).

Morbilliform reaction is the most common presentation of exanthematous drug eruption. Morbilliform is defined as a rash resembling measles and is clinically depicted by erythematous macules and/or papules, often coalescing into larger plaques. Many studies have shown that cutaneous biopsy alone cannot distinguish with certainly that a reaction is due to a drug. There are some clues that suggest the diagnosis: (i) Epidermis (mild spongiosis is the most consistent feature, with occasional hyperplasia of the epidermis. Few lymphocytes are commonly present in the epidermis. In 97% of biopsies, vacuolization was found in the dermoepidermal junction); (ii) Dermis (perivascular infiltrate is virtually always present, composed of lymphocytes and in 60% of cases scattered eosinophils); (iii) papillary dermal edema; (iv) dilated lymph and blood vessels.

The primary differential diagnosis for morbilliform eruptions includes viral exanthemas (e.g., EBV, HHV-6, and CMV), bacterial toxin resection (streptococcal or staphylococcal), Kawasaki syndrome, and others such as secondary syphilis, scarlet fever, acute HIV, or acute GVHD.

The treatment is supportive. The first measure is the withdrawal the causative agent. Topical corticosteroids and systemic antihistamines can be administered in the first step. If necessary, this can be combined with a short cycle of systemic corticosteroids (oral prednisone, 0.5 mg/kg/day, with progressively tapering dosages over several days). Antihistamines are indicated as adjuvant therapy in cases of itching.

Acute Urticaria and Angioedema [48–50]

Drug-induced urticaria is the second most common form of cutaneous drug reaction after exanthematous reactions.

Urticarial eruption can be broken down into simple acute urticarial eruptions, those involving angioedema or anaphylaxis, and serum sickness-like reactions as previously described in this chapter. Simple urticarial reactions caused by drugs consist of erythematous and edematous lesions, which have central clearing with a red border. The lesions can be located anywhere on the body and wax and wane over hours to days. Pruritus is an associated symptom. This type of drug reaction takes place minutes to days after exposure to the offending drug.

Common drugs responsible for urticarial reactions include antibiotics, such as penicillins, cephalosporins, sulfonamides, and tetracyclines, generally due to IgE-mediated hypersensitivity reaction. Another common class of drugs related to urticarial eruptions is nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs cause most frequently non-IgE-mediated urticaria and angioedema because of their pharmacologic activity of cyclooxygenase-1 enzyme inhibition, particularly of prostaglandin E2, and results in the generation of leukotriene C4 and activation of inflammatory cells.

Urticaria and angioedema are associated in about 50% of cases. Regarding ACE inhibitors, angioedema is described in 0.5% of patients treated with this class of drugs, and often without urticarial lesions. Rarely, angiotensin II receptor blockers result in the same complication.

Oral or injectable antihistamines and systemic corticosteroids are sometimes needed for severe acute urticaria and intramuscular epinephrine for angioedema. In cases of isolated angioedema caused by ACE inhibitors, epinephrine will not control the symptoms and it is necessary to use the selective bradykinin B2 receptor antagonist icatibant in this clinical setting.

Fixed Drug Eruptions [49, 51]

This entity is defined as recurrent lesions that, upon repeated uptake of the causative drug, always appear at the same skin or mucosal sites. FDEs present as well as circumscribed, single or multiple, often pruritic or burning erythematous, dusky patches (Fig. 26.21), ranging from several millimeters to over 10 cm in diameter. Vesicles or even blisters can develop. As the lesions resolve, they leave residual hyperpigmentation. The hallmark of FDEs is geographic memory. If a reaction recurs, it tends to recur in the same location as previously (although a new location can also be involved).

Lips, hands, genitalia (especially male genitalia), and occasionally oral mucosa are favored sites of FDE occurrence, although the lesions can be found anywhere on the skin and mucous membranes. After intake of the offending drug, FDE appears within minutes up to several hours (about 30 min to 8 h). The cutaneous lesions can be accompanied by general symptoms such as fever, nausea, dysuria, abdominal cramps, and diarrhea, though rarely. On occasion the disease presents in an atypical form with blunt-margined, non-pigmented, giant (>20 cm in diameter), urticarial, purpuric, targetoid, linear, reticular, and butterfly-like lesions.

The histopathologic hallmark is brisk interface dermatitis with varying amounts of epidermal necrosis as well as melanophages and eosinophils in the upper dermis. FDEs reveal a reaction pattern with lichenoid or erythema multiforme-like changes. Atypical histopathologic reaction patterns such as leukocytoclastic vasculitis, neutrophilic reaction, and a predominantly dermal reaction without pigment incontinence in what is termed nonpigmented FDE have been reported.

The pathogenesis of FDE is based on the new subclassification of delayed type IV immune reactions (Werner Pichler), a type IVc reaction. In this kind of immune response cytotoxic T cells play a predominant function, whereby autoaggressive $\alpha\beta^+CD8^+$ memory T cells persist intraepidermally in previous FDE sites and play a central role in new flare-ups during drug recall. Under drug exposition, keratinocytes are stimulated to participate in immune response through TNF-α and a rapid expression of ICAM-1 molecule, and then stimulate CD8$^+$ T cells to produce IFN-γ and

Fig. 26.21 Multiple lesions of fixed drug eruption in a patient taking a nonsteroidal anti-inflammatory drug

express FAS-FAS ligand in the epidermal basal layer to induce apoptosis of keratinocytes. On the other hand, transient intraepidermal migration of CD4^{+} T cells is capable of releasing a downregulation profile of IL-10, inducing suppression of the flare-up reaction in FDE.

Many drugs have been found to cause FDE, with common offenders including sulfonamides, NSAIDs (e.g., ibuprofen), allopurinol, barbiturates, hydroxyzine, laxatives, tetracycline, phenolphthalein, and feprazone. Usually there is only one causative drug (monosensitivity), although sometimes several drugs can induce FDEs in the same patient (multisensitivity). The most common multisensitivity is the cross-reaction between chemically related drugs such as tetracyclines. Less frequently, multisensitivity can occur because of polysensitivity, whereby two or more chemically unrelated drugs either induce the identical FDE lesion or each drug determine flare-ups in separate lesions.

Treatment is mainly symptomatic with discontinuation of offending agent, topical corticosteroids, and antihistamines.

Acneiform Eruptions [49, 52]

This kind of ADR produces lesions resembling acne vulgaris, but unlike acne vulgaris, drug-induced acneiform eruptions typically are not associated with the presence of comedones (blackheads and whiteheads). Acneiform drug eruptions appear as erythematous papules or erythematous pustules on the face and trunk (Fig. 26.22) and proximal extremities, but sometimes can be present on the forearms and legs, an unusual site in acne vulgaris. The most relevant hallmark is the monomorphous pattern of this eruption and the resolution without scarring. Drug-induced acneiform eruptions represent only 1% of drug eruptions.

Several medications are related to flare-ups of drug-induced acneiform eruptions, the most strongly associated being lithium, androgens, oral contraceptives, corticosteroids, vitamin B complex, and nowadays epidermal growth

Fig. 26.22 Acneiform eruption resulting from the combination of intramuscular injectable vitamin B complex and betamethasone for orthopedic pain

receptor (EGFR) inhibitors for chemotherapy. Iodine, bromide, isoniazid, actinomycin D, and phenytoin have also been associated. In the last decade, the use of supplementary complexes by bodybuilders, such as milk and whey protein-based products, have been reported as being involved in acneiform eruptions. This is an effect caused by elevations of postprandial insulin and basal insulin-like growth factor I plasma levels.

Treatment involves discontinuing the use of the offending drug, except in the case of EGFR inhibitors, when discontinuation may not be possible. Benzoyl peroxide, topical retinoids, and topical or oral antibiotics, such as doxycycline, can be used to treat the reaction, similar to the treatment of acne vulgaris.

Lichenoid Eruptions [49, 53]

Drug-induced lichenoid eruptions are uncommon ADRs that appear similar or even identical to lichen planus, with shiny violaceous polygonal papules and plaques (Fig. 26.23). Drug-induced lichenoid eruptions can present virtually anywhere on the body surface, but certain clues in the distribution can help suggest drug eruption over lichen planus. Drug-induced lichenoid eruptions tend to be absent from the flexor surface of the wrists, genitals, and mucous membranes, whereas these locations are often involved in common lichen planus. Lichen planus drug eruptions also often favor sun-exposed areas of the body.

Several drugs have been reported to be related to drug-induced lichenoid eruptions: gold salts, antimalarials, methyldopa, NSAIDs, penicillamines, lithium, sulfonylureas, phenylenediamine derivatives, thiazide diuretics, β-blockers, omeprazole, and pantoprazole. The time from initiation of the drug to onset of lichenoid drug eruption varies greatly

Fig. 26.23 Lichenoid drug eruption

depending on the causative medication. Reactions caused by naproxen, for example, tend to occur approximately 10 days after administration. By contrast, certain drugs such as lithium, methyldopa, and acebutolol can develop lichenoid eruptions several years later. HIV infection can contribute to lichenoid drug eruptions on photoexposed areas of the body.

Treatment typically is symptomatic, with topical corticosteroids a mainstay. Once discontinuation of the medication has been accomplished, the eruption resolves spontaneously after a period of a few weeks or months.

Photosensitivity Reactions [54–56]

Acute photosensitivity ranges from common polymorphous light eruptions to phototoxicity, or rare photoallergies. Photosensitivity refers to reactions that occur when a photosensitizing agent (chromophore substance) in or on the skin reacts with ultraviolet (UV) radiation, often in doses smaller than those associated with sunburn. Up to 8% of cutaneous drug reactions are photosensitivity eruptions. Typically, a photosensitivity reaction occurs within hours to days of exposure to sunlight and may last for up to 1 week or more.

More frequent reactions are named "phototoxic reactions," in which skin signs resemble moderate to severe sunburn, with erythema, blistering, weeping, and desquamation. Photoallergic reactions resemble eczematous lesions, often in subacute or chronic presentation. Phototoxic and photoallergic reactions occur in sun-exposed areas of the skin; however, widespread eruptions can occur, which may suggest a systemic photosensitizing agent (photoallergy).

These reactions are dose related and are most commonly seen in patients who have been exposed to high doses of both the drug and UV radiation. One's susceptibility to this type of syndrome is variable and likely based on drug absorption and metabolism, as well as the amount of melanin in the skin.

Piroxicam, fluoroquinolone antibiotics, tricyclic antidepressants, and NSAIDs are classes
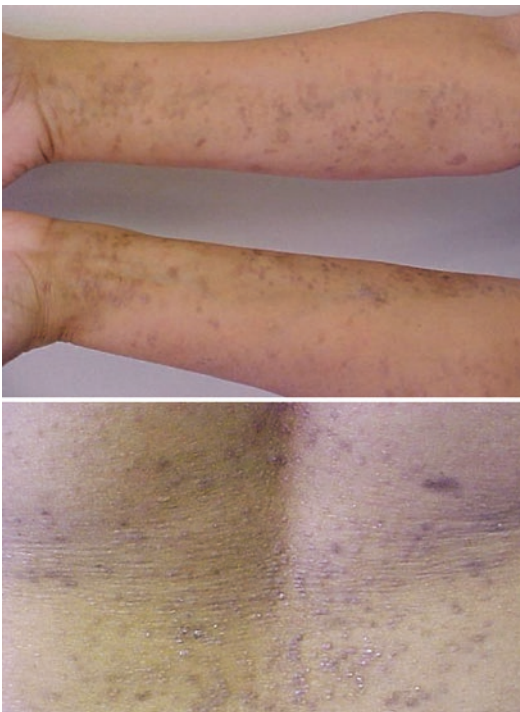
Fig. 26.24 Photosensitivity due to voriconazole causing severe cheilitis

of drugs that have been reported to be frequent photosensitizers, with fluoroquinolones being the most potent. Other antibiotics, such as TMP-SMX and tetracyclines, have also been implicated. Recently voriconazole, a third generation of azole antifungal agents, has been reported as a photosensitivity agent, especially in phototoxic reactions (Fig. 26.24), in 8% of outpatients treated, besides increasing the potential of nonmelanoma skin cancer (particularly squamous cell carcinomas) arising from potential photocarcinogenesis related to voriconazole.

Phototoxic reactions are the most common dermatologic adverse effect of amiodarone therapy, affecting 25–75% of patients on long-term treatment. Photoallergy is considerably less likely to occur, but the risk also increases with prolongation of the therapy. Skin changes usually occur after at least 4 months of therapy and with the minimal cumulative dose, which is 40 g.

Management of photosensitivity reactions includes limiting exposure to sunlight, using potent sunscreen, and wearing protective clothing. Oral and topical corticosteroids agents may be employed in the treatment.

Drug-Induced Coma Blisters [57, 58]

Coma blisters are uncommon skin eruptions seen in patients with impaired consciousness. The original case was described in a patient who was heavily sedated because of barbiturate intoxication. Subsequently anticonvulsants have been reported, including certain benzodiazepines such as clobazam (Fig. 26.25), and valproic acid and amitriptyline overdose. There were a few reports of coma blisters and peripheral neuropathy caused by amitriptyline overdose. These blisters are most often seen in pressure areas, particularly over bony prominences in contact with hospital beds.

The hallmark histologic feature that defines coma blisters is eccrine gland necrosis in the skin. Differential diagnosis with bullous pemphigoid is obtained with a negative direct immunofluorescence biopsy of the skin. Until recently, coma blisters were thought to be a self-limiting process that did not require withdrawal of the offending agent. However, in some patients the eruption resolves only upon withdrawal of the drugs.

Fig. 26.25 Coma blisters in forearm of a patient with stroke under medication with barbiturates
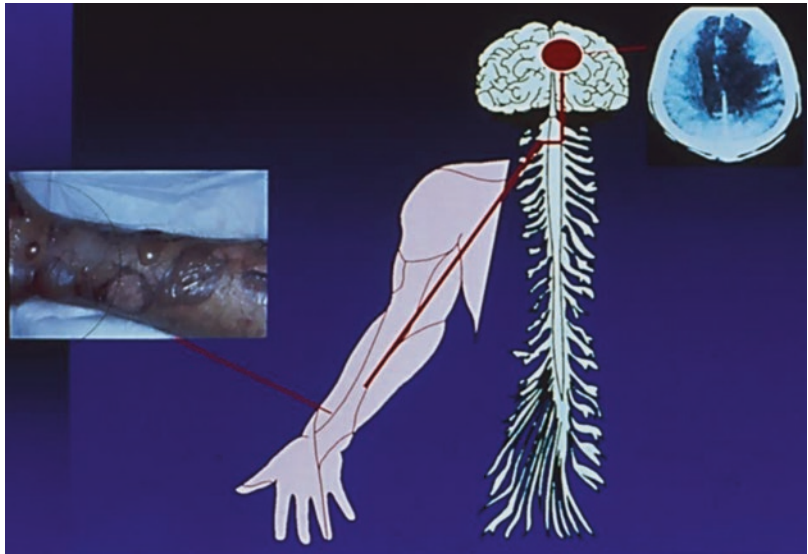
Drug-Induced Erythema Nodosum [59]

Erythema nodosum is a skin reaction manifested by tender or painful erythematous subcutaneous nodules, located usually on the extensor aspects of the lower extremities. Histologically it is a septal panniculitis without vasculitis. Several conditions can be induce and act as an antigenic stimuli, including drugs, benign and malignant systemic diseases, leprosy, and bacterial (e.g., tuberculosis) and fungal infections. Frequently the cause is unknown.

Drugs that may cause erythema nodosum are antimicrobial agents (amoxicillin, penicillin, sulfonamides), bromide, iodine, gold salts, analgesics and antipyretics (including paracetamol), carbimazole, isotretinoin, azathioprine, vemurafenib, GM-CSF, oral contraceptives (estrogens/progesterones), and estrogens. Erythema nodosum disappears within a couple of weeks after withdrawal of the causative drug.

Drug-Induced or Exacerbating Psoriasis [57, 60]

Drug-induced psoriasis is well documented. Such eruptions may occur in patients with pre-existing

Fig. 26.26 Psoriasis exacerbation after using anti-TNF-α agents

psoriasis (exacerbation phenomenon) or those without a personal or family history. Lesions typically improve with drug withdrawal, although persistent disease is possible. More frequent drugs involved are β-blockers, lithium, antimalarials, NSAIDs, anti-TNFα agents (Fig. 26.26), and bupropion.

Exacerbation of psoriasis caused by the following medications has also been observed: adrenergic antagonists, IFN, gemfibrozil, iodine, digoxin, and clonidine.

Symmetric Drug-Related Intertriginous and Flexural Exanthema [61]

In individuals previously sensitized to an allergen through contact, systemic exposure results in the development of a condition classically termed systemic contact dermatitis. One of the most common manifestations of this condition is so-called baboon syndrome (BS).

A subsequent study by Hausermann et al. [62] examined a series of 100 cases of BS and found that about half of the patients exhibited no evidence of prior skin sensitization. For that group the authors proposed the term "symmetric drug-related intertriginous and flexural exanthema" (SDRIFE) to describe a peculiar form of drug rash with symptoms similar to those of true BS.

BS is historically often equated with a mercury-induced exanthem in patients with previous contact sensitization. SDRIFE specifically refers to the typical clinical pattern of this drug eruption, and the following diagnostic criteria are proposed [62]: (1) exposure to a systemically administered drug either at the first or repeated dose (excluding contact allergens); (2) sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area; (3) involvement of at least one other intertriginous/flexural localization (Fig. 26.27); (4) symmetry of affected areas; and (5) absence of systemic symptoms and signs.

Several drugs are reported to induce SDRIFE [63]: (i) β-lactam antibiotics (amoxicillin, ampicillin, amoxicillin/clavulanic acid, pivampicillin, penicillin V, ceftriaxone, cefuroxime, cephalexin) and non-β-lactam antibiotics (including clindamycin, roxithromycin); (ii) corticosteroids: deflazacort; (iii) radiocontrast barium; (iv) other drugs: sulfate iomeprol, iopromide, monoclonal antibodies (cetuximab, glembatumumab), vedotin (CR011, vcMMAE), psychopharmaceuticals (risperidone loflazepate ethyl), allopurinol, cimetidine hydroxyurea, heparin (intravenous), IVIG, mitomycin C, naproxen, oxycodone, pseudoephedrine, salsalate, terbinafine, and valacyclovir.

Nicolau Syndrome or Embolia Cutis Medicamentosa (ECM) [64, 65]

In 1924, Freudenthal described full-thickness dermal necrosis associated with intramuscular injection of oily bismuth suspension, which was

Fig. 26.27 Symmetric drug-related intertriginous and flexural exanthema (axillae and groin)

used to treat syphilis at that time. He described the histologic appearance of these suspended particles deep within the cutaneous arteries, distant from the injection site. This condition was also described by Nicolau the following year, and the syndrome more often bears his name despite Freudenthal's precedence in the literature.

Nicolau syndrome is an iatrogenic syndrome caused by intramuscular injection leading to variable degrees of tissue necrosis, with variable severity, including the skin and deeper tissues. Intense pain in the immediate postinjection period and purplish discoloration of the overlying skin, with or without a reticulate pattern (livedo racemosa-like pattern), is highly characteristic of this syndrome. Intramuscular, subcutaneous, intravenous, and intra-articular injections have been reported to produce this syndrome. The skin necrosis resolves with severe and disfiguring scarring. It is therefore important that dermatologists and cutaneous surgeons are aware of this agonizing and deforming iatrogenic complication of injections.

Discoloration of the skin may result in necrosis and ulceration, which might involve the subcutaneous tissue and the muscular layer. Paralysis of the lower extremities has been reported and attributed to embolization of the medication, mainly resulting from the force of injection from the gluteal vessels into the internal iliac arteries, and ischemia of sciatic nerve. Application of cold devices or compress tends to aggravate the tissue injury and necrosis.

Several drugs are related to ECM: (i) intramuscular injections (vitamin K, NSAIDs, hydroxyzine, vaccination, bismuth, benzathine penicillin, penicillin G); (ii) intravenous injections (polidocanol 1%); (iii) subacromial injection (triamcinolone acetate); (iv) subcutaneous injection: pegylated IFN-α, glatiramer acetate; and (v) intra-articular: glucocorticoid.

Aspirating just before injecting has been suggested as a method of preventing Nicolau syndrome, as it is thought to help prevent embolism caused by intra-arterial deposition of medication. However, it is doubtful as to whether Nicolau syndrome can be prevented by this method, as the spasm of the vessel or vasocompressive effect in Nicolau syndrome is usually difficult to recognize.

The essential difference between those cases of ECM and the pathophysiology seen with vascular obstruction by dermal fillers (hyaluronic acid, polymethylmethacrylate microspheres) is that the former often involves inflammatory pathways being activated by the injected material, whereas the latter typically involves a more purely mechanical vascular obstruction (although some dermal fillers may promote blood clotting, hyaluronic acid-based dermal fillers by design are minimally reactive in tissues). The phenomena are similar in that the inciting event is accidental intravascular injection, followed by some degree of intravascular transport, finally resulting in distal vascular obstruction, ischemia, and so forth, such that the ultimate clinical presentation is the same.

Diagnosis is mainly clinical; cutaneous biopsy reveals necrotic changes caused by ischemia. Ultrasonography study of the skin and magnetic resonance imaging help in delineating the extent of damage. Prompt treatment has been reported to avert necrosis of the skin. In the immediate post-event period, treatment is based on various approaches to improve blood supply such as pentoxyphylline, hyperbaric oxygen, intravenous alprostadil, and thrombolysis with heparin. Intralesional corticosteroid has also been used to reduce inflammation. Surgical debridement of the necrotic scar is of utmost importance as it reduces infection and enhances wound healing.

Drug-Induced Linear IgA Bullous Dermatosis (LABD) [49, 66]

LABD often presents a singularity in its presentation. It has been reported that almost two-thirds of LABD cases may be drug induced, although this is rare in children, in whom LABD behaves as an idiopathic autoimmune blistering disease.

The clinical picture consists of an acute development of vesicles and bullous lesions often on sites of noninflamed skin. Typically, new lesions develop around previous lesions forming rosette-like plaques, widely distributed on the face, trunk, and extremities, especially around the perioral and genital areas. Mucosal involvement in drug-induced LABD is less common than in

the autoimmune form. The most commonly used medication associated with this kind of ADR is vancomycin; however, other drugs include amiodarone, atorvastatin, captopril, ceftriaxone, diclofenac, furosemide, lithium, metronidazole, penicillin, phenytoin, piroxicam, rifampin, and trimethoprim-sulfamethoxazole.

Treatment of drug-induced LABD includes discontinuation of the causative agent and treatment with topical or systemic steroids, dapsone, and/or nonsteroidal systemic immunosuppressive agents.

Drug-Induced Bullous Pemphigoid [49]

This entity is very similar to the autoimmune form. Multiple tense bullous lesions appear on the skin and pruritus is a common symptom. Often the medications associated with drug-induced bullous pemphigoid include furosemide, ACE inhibitors (especially captopril and enalapril), penicillin, ampicillin, chloroquine, psoralen-UVA treatment, and sulfasalazine.

Treatment is aimed at discontinuation of the offending drug as well as topical or systemic corticosteroids and steroid-sparing immunosuppressive drugs as indicated.

Drug-Induced Pemphigus [49]

Similar other drug-induced reactions related to counterpart autoimmune conditions, drug-induced pemphigus most closely resembles pemphigus foliaceus, with flaccid vesicles or bullae that rupture, creating crusted or desquamated erosions, with mucous membranes often spared.

The histologic hallmark of this drug-induced eruption is the acantholysis of epidermal cells, but this phenomenon is not a pathognomonic sign of this type of ADR. Both autoimmune (idiopathic) and drug-induced pemphigus have a positive Nikolsky sign, as observed in the SJS/TEN spectrum, although SJS/TEN does not demonstrate acantholysis in the skin biopsy.

Drugs containing thiol molecules (penicillamine, thiopurine, pyritinol, gold sodium thiomalate, captopril) are responsible for 80% of the cases, and other drugs implicated include levodopa, penicillin, phenobarbital, piroxicam, propranolol, and rifampicin. Drug-induced pemphigus can occur any time within the first year of initiation of one of the offending drugs. Treatment generally consists of withdrawal of the drug and use of systemic corticosteroids.

Adverse Mucocutaneous Reactions to Chemotherapeutic Drugs [44, 67–70]

The skin, mucous membranes, annexes (sebaceous and sudoriferous glands), and the phaneros (hair and nails) are tissues with rapid cellular proliferation and are thus susceptible to adverse reactions (toxic or hypersensitive) resulting from systemic chemotherapeutic treatment.

Antineoplastic agents are defined as substances that inhibit or prevent the proliferation of neoplasms. Because of their high metabolic rate, the skin, mucous membranes, and annexes are the most important target organs of the toxicity associated with chemotherapy. Reactions can present with disseminated exanthematous eruptions, nonspecifically, or as distinct cutaneous lesions. Some drugs can trigger localized reactions caused by extravasation to tissues adjacent to the areas of application.

Exanthematous reactions, such as nonspecific erythema multiforme, are more common, and many of them are attributed to hypersensitivity mechanisms. Certain local toxicity, such as alopecia, mucositis, nail alterations, or hand-foot syndrome, is more specific and less common, frequently associated with particular drugs or groups of drugs.

The identification of the reaction pattern associated with the trigger drug and of the possible dose-limiting toxicity is of extreme importance to the physician, as is the differential diagnosis with infectious processes and specific manifestations of the neoplasm.

Alterations of the Phaneros and Cutaneous Annexes [44, 67–70]

Alopecia [44, 67–70]

Alopecia is the most common adverse skin manifestation of chemotherapeutic treatment. There are two types of drug-induced alopecia: the anagen effluvium and the telogen effluvium. In the anagen effluvium hair loss occurs because of the sudden interruption of the mitotic activity of the hair matrix, 1–2 weeks after the start of chemotherapy, leading to lack of hair production or its thinning (Pohl–Pinkus constrictions). The weakening of the hair shaft in this context predisposes the hair to breakage and shedding during the act of combing. They involve the hair, eyebrows, beard, axillary hair, and pubic hair. It is dose-dependent and reversible. New hairs often grow back with a different color and texture. In the telogen effluvium, hairs move prematurely to a resting phase with subsequent loss of normal hair.

The antineoplastic agents that most frequently cause the anagen effluvium lead to diffuse hair loss, of sudden onset, from 7 to 10 days after the start of chemotherapy. Hair loss becomes more pronounced about 1–2 months after the start of treatment. Even though hair loss is intense, about 10% of the pilous follicles are usually in a resting phase at the time of the administration of the drug, and this determines incomplete hair loss. With repeated treatment cycles, alopecia totalis may occur. This type of effluvium is generally reversible when treatment is suspended, and occasionally permanent with the use of cyclophosphamide and busulfan. Hair grows around 1 cm per month, possibly showing new texture and color. The chemotherapeutic drugs more often associated with alopecia when used in isolation are: (i) complete alopecia (cyclophosphamide at high dose, doxorubicin, docetaxel, dactinomycin, irinotecan, topotecan, bleomycin, paclitaxel); (ii) incomplete alopecia (etoposide, ifosfamide, mitomycin C, 5-fluorouracil, melphalan, mitoxantrone, gemcitabine, vinca alkaloids).

Most reactions can be reversed by dose reduction or by increasing the interval between doses. Some toxic effects can be successfully treated or prevented. Medication administered before the chemotherapeutic treatment can prevent hypersensitivity reactions. The use of oral antiseptic solutions is useful in the control of mucositis.

Some dermatologic reactions to new antineoplastic agents, such as EGFR inhibitors, have been associated with anticancer efficacy.

Other adverse effects may be mistaken for reactions to chemotherapeutic drugs and include infections resulting from immunosuppression, paraneoplastic syndromes, GVHD, nutritional deficiencies, development of skin malignancies, and metastatic primitive tumor.

There are several classifications of reactions to antineoplastic drugs. The lack of a systematized multidisciplinary approach does not provide all the microscopic data and physiopathogenic mechanisms that delineate the lesions. Therefore, the classification adopted didactically groups with the eruptions based on the target cells and mechanism of action of the drugs.

Preventive measures to limit hair loss have had limited success. Hypothermia of the hair scalp or tourniquets applied in this region may reduce the perfusion of the drug in the pilous follicles and delay the start of or minimize hair loss. This procedure is contraindicated for patients with hematologic neoplasms such as leukemias, lymphomas, and other potentially metastatic tumors of the hair scalp. Topical minoxidil is not effective in the prevention of drug-induced alopecia, but may shorten its duration.

Trichomegaly and Hair Curling [44, 67–70]

Hair alterations with acceleration of growth and shaft changes are observed with the use EGFR inhibitors (Fig. 26.28).

Ungual, Subungual, and Periungual Alterations [44, 67–70]

Nail alterations can present with a reduction of the nail growth speed, fragility, lines of discoloration (Mees' lines), transversal depressions (Beau's lines), hyperpigmentation, onycholysis with subungual aseptic abscesses, photo-onycholysis, paronychia, and pyogenic granulomas of the periungual folds. Nearly all antineoplastic agents

Fig. 26.28 Blepharitis and trichomegaly caused by cetuximab (image under dermoscopy, ×10)

Fig. 26.29 Ingrown nail and pyogenic granuloma in a patient using erlotinib

can lead to reduction of growth speed, nail fragility, Mees' lines, and Beau's lines.

Hyperpigmentation can occur after the use of cyclophosphamide, hydroxyurea, fluoropyrimidines such as 5-fluorouracil, and especially anthracyclines such as doxorubicin and daunorubicin. Painful onychomycosis and subungual abscesses are due to the use of taxanes (docetaxel/paclitaxel) and anthracyclines (doxorubicin).

Ingrown nails, paronychia, and pyogenic granuloma are associated with the use of tyrosine kinase inhibitors of EGFR (Fig. 26.29), such as erlotinib and gefitinib. The fenestration or avulsion of the lamina should be considered when abscesses that involve more than 50% of the nail bed are present. In these more severe cases, the temporary suspension of treatment, longer

intervals between cycles, and dose reduction should be considered.

Neutrophilic Eccrine Hidradenitis [44, 67–70]

This rare, nonspecific disease often occurs when chemotherapeutic drugs are used in combination, making it difficult to know which drugs are responsible for causing the disease.

Cytarabine is the most commonly cited drug; however, others are also implicated, such as bleomycin, chlorambucil, cyclophosphamide, cytarabine, doxorubicin, lomustine, mitoxantrone, busulfan, carmustine, cisplatin, cyclophosphamide, etoposide, 5-fluorouracil, methotrexate, and thiotepa. Some authors consider neutrophilic eccrine hidradenitis (NEH) as a paraneoplastic phenomenon, since it has been found in an early case of acute myeloid leukemia not yet treated. It has been associated with HIV infection, *Nocardia*, *Serratia*, *Enterobacter*, *Staphylococcus*, and with patients receiving GM-CSF. The mechanism is unknown, but may be due to the excretion of the chemotherapeutic drug by the eccrine glands and its direct toxic effect on the eccrine epithelium.

The clinical condition may be preceded by fever and unspecific clinical signs. Skin eruptions are distributed in the head, neck, trunk, and extremities, with lesions that vary from erythema, papules, nodules, and pustules to papular plaques. Lesions may be purpuric or hyperchromic, single or multiple. They appear between 2 days and 3 weeks from the start of treatment, regressing spontaneously without scarring or sequelae 1–4 weeks after the suspension of the drug.

The differential diagnosis is vast and includes sepsis, septic embolism in a post-chemotherapeutic neutropenic patient, vasculitis, leukemia cutis, hypersensitivity reaction, urticaria, polymorphous erythema, and neutrophilic dermatoses such as Sweet's syndrome, bullous pyoderma gangrenosum, and atypical pyoderma gangrenosum.

Owing to the unspecific clinical presentation of the disease and the great number of differential diagnoses, some authors suggest that NEH be included in the diagnostic hypotheses of any

eruption that may occur in patients undergoing chemotherapy, and its final diagnosis is established by histopathology. Therefore, histopathology is essential for conclusive diagnosis. It is constituted by a dense neutrophilic infiltrate, inside and around the eccrine glands, with necrosis of the eccrine epithelium cells. Involvement of the apocrine glands has been reported. Occasionally, squamous syringometaplasia, hemorrhage and edema of the dermis, spongiosis and/or vacuolization of the basal layer of the epidermis, necrosis of keratinocytes, and mucin deposits inside and around the eccrine glands may occur.

In patients with severe neutropenia, the neutrophilic infiltrate may be absent; however, necrosis of the eccrine epithelium is typical. NEH is a self-limiting adverse reaction. Frequently the process resolves within a month, without treatment. In other chemotherapy cycles, 60% of the patients may relapse. The efficacy of the prophylactic or therapeutic use of systemic corticosteroids, dapsone, or nonhormonal anti-inflammatories is still questionable.

Eccrine Squamous Syringometaplasia
[44, 67–70]

Eccrine squamous syringometaplasia is an unusual adverse reaction to chemotherapeutic drugs. It can also be found in association with chronic ulcerations, skin tumors, exposure to toxic agents, and several inflammatory processes. Therefore, it is not a histopathologic reaction exclusive to the use of chemotherapeutic drugs. The mechanism of neutrophilic eccrine hidradenitis is unknown, but it can be the result of the excretion of the drug by the eccrine glands and its direct toxic effect on the eccrine epithelium. It is postulated that eccrine squamous syringometaplasia represents the final noninflammatory spectrum of adverse reactions to chemotherapeutic drugs in the eccrine glands.

Similarly to NEH, eccrine squamous syringometaplasia also has an unspecific clinical presentation, constituted by erythematous maculae, papules, and papular plaques or vesicles, localized or disseminated. Lesions develop between 2 and 39 days after the start of chemotherapy and improve spontaneously after 4 weeks.

The diagnosis is histopathologic, characterized by the presence of squamous metaplasia of the eccrine glands in the papillary dermis. Minimal and focal necrosis of the eccrine gland epithelium, fibroblastic proliferation, and edema of the periductal stroma may occur. Contrary to NEH, the neutrophilic infiltrate is minimal or absent. Squamous eccrine syringometaplasia has been described as an accidental histologic finding in other conditions not associated with chemotherapy.

Eccrine squamous syringometaplasia does not appear to be associated with a specific chemotherapy agent or malignancy. Numerous drugs have been related such as cytarabine, mitoxantrone, daunorubicin, cisplatin, 5-fluorouracil, doxorubicin, cyclophosphamide, etoposide, methotrexate, busulfan, melphalan, and carmustine.

Eccrine squamous syringometaplasia has been observed in association with palmoplantar erythrodysesthesia syndrome, in radiation-induced memory reactions, and in patients who underwent bone marrow transplantation and received high doses of chemotherapeutic drugs. The condition often spontaneously resolves.

Acral Erythema or Palmoplantar Erythrodysesthesia Syndrome [44, 67–70]

First described in 1974, this syndrome is also known as Burgdorf's syndrome, palmoplantar erythema, hand-foot syndrome, and toxic erythema of the palms and soles. It occurs more frequently in patients treated with cytarabine and, fluoropyrimidines, especially capecitabine, which is the oral 5-fluorouracil prodrug.

After alopecia and mucositis, it is the most common adverse reaction to chemotherapy. Other agents less frequently associated with palmoplantar erythrodysesthesia syndrome are cisplatin, cyclophosphamide, cytarabine, doxorubicin, daunorubicin, doxifluridine, etoposide, floxuridine, hydroxyurea, mercaptopurine, methotrexate, mitotane, paclitaxel, docetaxel, and vinorelbine.

It is estimated that this adverse reaction occurs in 6–64% of the patients treated with different chemotherapeutic regimens.

Most patients show a prodrome of dysesthesia, with a tingling (pins and needles) sensation on the palms and soles. Within a few days the reaction evolves to a feeling of pain and burning with a well-demarcated edema and erythema. The erythema is symmetric and sometimes more pronounced on the soft parts of the distal phalanges. Hands are often more affected than feet (Fig. 26.30a). Some patients show light scaling with or without erythema. A bullous variant has been described (Fig. 26.30b), representing a more severe form of the reaction, specifically associated with cytarabine and methotrexate. Lesions are aggravated if the treatment is not suspended, and the associated pain and edema may limit the movement of fingers. When the drug is suspended, the reaction progressively improves within 2 weeks.

In some patients, when treatment is maintained despite the development of erythrodysesthesia syndrome, palmoplantar keratodermia may occur. The reaction occurs more frequently in patients who undergo oral or continuous infusional therapy with fluoropyrimidines (2–18%), as compared with those submitted to bolus therapy (0.4–3%).

It is thought that in the pathogenesis of the process the local accumulation of the drug leads to degeneration with necrosis of the sweat glands, because its microscopic aspects are similar to those of eccrine squamous syringometaplasia and neutrophilic eccrine hidradenitis.

In the differential diagnosis the following should be considered: polymorphous erythema, erythromelalgia, eccrine squamous syringometaplasia, and neutrophilic eccrine hidradenitis. The most relevant differential diagnosis is acute GVHD. The fundamental difference is that acute GVHD occurs in patients who have received a bone marrow transplant, in addition to extracutaneous involvement with gastrointestinal alterations (abdominal pain and diarrhea, elevation of hepatic enzymes). In cases of acute GVHD without extracutaneous manifestations, differentiation may be difficult.

Nevertheless, acute GVHD presents with diffuse erythema and can form papules, whereas palmoplantar erythrodysesthesia syndrome shows a well-demarcated erythema and edema. There are no relevant histopathologic differences between them, except for necrosis of the satellite cell in all layers of the epidermis (apoptotic keratinocytes adjacent to lymphocytes) in acute GVHD and sometimes presence of squamous syringometaplasia in palmoplantar erythrodysesthesia syndrome. The differentiation between these two disorders is essential because the use of cyclosporine is necessary to treat acute GVHD, but worsens the patient's pain if used in the treatment of palmoplantar erythrodysesthesia.

Apart from dose reduction, longer intervals between the cycles of chemotherapy and, as a last resort, the suspension of the drug, there is no specific treatment for palmoplantar erythrodysesthesia syndrome that has proved to be effective in a large series of cases. Some treatments have been suggested for small series of patients or case reports. General measures should be taken, such as reduction or suspension of the drug, longer intervals between chemotherapy cycles, dressings, elevation of the extremity, cold compresses, analgesic medication, and emollients.

As a specific treatment, pyridoxine can be used if 5-fluorouracil, liposomal doxorubicin, doxorubicin, docetaxel, and etoposide have been administered; hand cooling (docetaxel); oral corticosteroids (doxorubicin, 5-fluorouracil); strong topical corticosteroids (liposomal doxorubicin, cisplatin, and 5-fluorouracil); and topical dimethyl sulfoxide (DMSO) at 99% (liposomal doxorubicin). Symptoms can be relieved with lesion care to prevent infection and elevation of the limb to reduce the edema.

Cooling of hands and feet during treatment reduces the blood flow in these areas and may decrease the severity of the reaction. Strong topical corticosteroids have been used with mixed results when associated with emollients. Systemic corticosteroids are useful in some situations. Pyridoxine (vitamin B6) in doses of 200–300 mg/day can be useful to treat and prevent this reaction, except when cytarabine or vincristine is used. Topical DMSO at 99% four times a day for 14 days has cured some cases of palmoplantar erythrodysesthesia syndrome induced by pegylated liposomal doxorubicin.

Toxic Erythema Caused by Chemotherapeutic Drugs [44, 67–70]

Some authors prefer to associate toxic erythema caused by chemotherapy with clinical lesions that present with painful erythema, with or without edema, often affecting the hands and feet, intertriginous areas such as the axillary and inguinal regions, and less frequently the elbows, knees, and auricular pavilion. These eruptions may have a bullous component, are self-limited, and generally evolve with resolution and scaling associated with postinflammatory hyperpigmentation.

Many denominations used refer to histopathologic findings or those given by various authors on different occasions. Disorders such as eccrine squamous syringometaplasia, NEH, acral erythema, and palmoplantar erythrodysesthesia syndrome would be, according to these authors, grouped under toxic erythema caused by chemotherapeutic drugs.

The objective to group many disorders under the same denomination seeks to emphasize the superposition of clinical characteristics and promote an easy dialogue between medical specialties and with the patient.

The clinical characteristics of the toxic erythema associated with chemotherapy are: (1) maculae or erythematous and/or edematous plaques on the hands and feet, intertriginous areas, and less frequently on the elbows, knees,

and auricular pavilions, often appearing 2–3 days after the administration of the drug; (2) associated symptoms of pain (that may be debilitating), burning, paresthesia, pruritus, and/or hypersensitivity; (3) pale color, petechiae, and/or sterile blisters, followed by erosion in areas of intense erythema; (4) scaling and spontaneous resolution without specific treatment; and (5) chance of relapse if an equal or higher dose is administered.

Isolated papules may be found in the periphery of plaques. Papules and plaques may also be found in the head, cervical region, trunk, and extremities. Onset of lesions after 2–10 months can be observed.

The histologic characteristics observed are atypia (larger cells and nuclei and nuclear pleomorphism), apoptosis of keratinocytes, mitotic figures and bizarre mitotic configurations (astral mitosis), loss of polarity of the epidermal cells and apoptosis of keratinocytes, vacuolar degeneration of the basal layer of the epidermis, dermal edema, and eccrine squamous syringometaplasia. Moreover, necrosis of the upper epidermis, similar to the alterations observed in pellagra, may also occur. The inflammatory infiltrates are usually minimal despite their abundant clinical profile. From these observations, it has been suggested that erythema is secondary and results from damage to keratinocytes, leading to the release of cytokines and vasodilation.

Acneiform Eruption [44, 67–70]

Acneiform eruption is the adverse effect more often associated with the use of EGFR inhibitors. Onset occurs 1 week after the start of treatment with the EGFR inhibitor as a self-limiting eruption, dose-related, that affects the face, central region of the thorax, upper dorsum and, more rarely, limbs.

It presents with follicular erythematous papules, pustules with or without comedones, and scaling of the interfollicular skin (Fig. 26.31). Often an association with the following conditions is observed: acral asteatosis, paronychia with pyogenic granuloma, oral and nasal aphthous ulcerations, and hair alterations.

Palms and soles are often free of lesions. Excessive follicular hyperkeratosis leading to the

Fig. 26.31 Cetuximab-induced acneiform eruption on trunk

obstruction of the ostium with formation of a follicular corneal plug, rupture of the glandular wall, and consequent inflammatory process are suggested as pathogenic mechanisms.

In the histopathologic examination a prominent corneal plug, with dilated infundibulum, with or without neutrophilic folliculitis, is observed. There is a positive correlation between the severity of the eruption and the tumoral response and survival. We emphasize the need for attention to the eruption to improve adherence to the chemotherapeutic treatment. The use of topical anti-acne agents and oral tetracyclines improve the condition. Topical emollients are indicated to treat xerosis.

Mucous Membrane Alterations [44, 67–70]

Stomatitis [44, 67–70]

Oral mucositis is the main dose-limiting reaction of most chemotherapeutic drugs. About 40% of the patients being treated show some type of oral complication. These complications are often associated with drugs that affect the synthesis of DNA. The main causative agents are antimetabolic drugs and antitumoral antibiotics.

The drugs more frequently associated with stomatitis are bleomycin, dactinomycin, methotrexate, topotecan, and 5-fluorouracil. Unusually, the stomatitis caused by 5-fluorouracil is related to its continuous infusional administration or to the use of its oral prodrug, capecitabine, and is less frequently observed when 5-fluorouracil is administrated in bolus. The main mechanism is the direct toxicity of the drug, but it can result secondarily from the indirect effects of the drug on the bone marrow. In patients with head and neck tumors, cisplatin used during radiotherapy acts as a strong radiosensitizer. In these cases there is more tumoral control but also greater severity of stomatitis caused by a boost in the direct effect of radiotherapy.

Since oral epithelium cells have a high mitotic index (renewal every 7–14 days), they become susceptible to the toxic effects of chemotherapeutic drugs. Moreover, there is atrophy of the oral mucosa, causing odynophagia, burning, xerostomia, and mucous membrane ulcerations. Ulcerations may be initially focal and then become diffuse and confluent, with occasional vesicles and blisters. These alterations are more common in the nonkeratinized mucosa and appear 4–7 days after use of the drug. Resolution of lesions may occur after treatment is suspended, often within 3–4 weeks.

Spontaneous or induced hemorrhage, especially gingival, may occur when the platelet count is below 10,000/mm^3. Patients at a higher risk of developing stomatitis are those with hematologic neoplasms, those who are under 20 years old (high mitotic activity of the epithelium), and patients with pre-existing oral disease and poor mouth hygiene.

Preventive measures include proper maintenance of oral hygiene by washing the mouth with water, saline solution, sodium bicarbonate, or hydrogen peroxide. The use of cold water to prevent mucositis induced by 5-fluorouracil and melphalan in high doses appears to be helpful. Other alternative clinical procedures, still not fully proven, consist in the use of chlorhexidine gluconate, β-carotene, and benzydamine chlorhydrate or sucralfate.

Treatment essentially consists of support with oral care, using agents such as magnesium or aluminum hydroxide and vitamin E. In addition, pain-relief drugs such as paracetamol and opioids (codeine and morphine) may be necessary when the use of topical anesthetics such as benzocaine and lidocaine are not effective. Additional complications occur because of secondary bacterial, viral, or fungal infections that may become systemic.

Palifermin, when used prophylactically, reduces the occurrence and duration of severe stomatitis in patients with hematologic tumors and submitted to bone marrow transplantation. Palifermin is a human recombinant factor of keratinocyte growth and protects various epithelial tissues. It acts not only on stomatitis but also on mucositis in general. A possible tumoral stimulating factor still limits its use in patients with epithelial tumors.

Scrotum Ulcer After Intraperitoneal Hyperthermic Chemotherapy with Mitomycin C [71–73]

Peritoneal carcinomatosis frequently signals the terminal stage in some cancers of gastrointestinal and gynecologic origins. Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy was introduced in the early 1990s and has become the mainstay of treatment in particular clinical settings for patients with peritoneal carcinomatoses, especially in pseudomyxoma peritonei, significantly improving overall survival rates.

There are four case reports of this recently described entity using a new procedure to treat peritoneal carcinomatosis after intraperitoneal hyperthermic chemotherapy with mitomycin C. One of them was described [71] in a male patient after 9 days of the procedure. The patient developed pain and scrotal necrosis on the anterior aspect of the scrotum (Fig. 26.32).

Two possible causes of the scrotal ulcers were proposed. (i) A patent processus vaginalis, allowing mitomycin C to become sequestered in the scrotum, inducing an inflammatory reaction, resulting in scrotal wall inflammation and subsequent ulceration (Fig. 26.33). This was proposed since previous studies have shown that intradermal

Fig. 26.32 Scrotal necrosis on anterior aspect of scrotum caused by intraperitoneal hyperthermic chemotherapy with mitomycin C
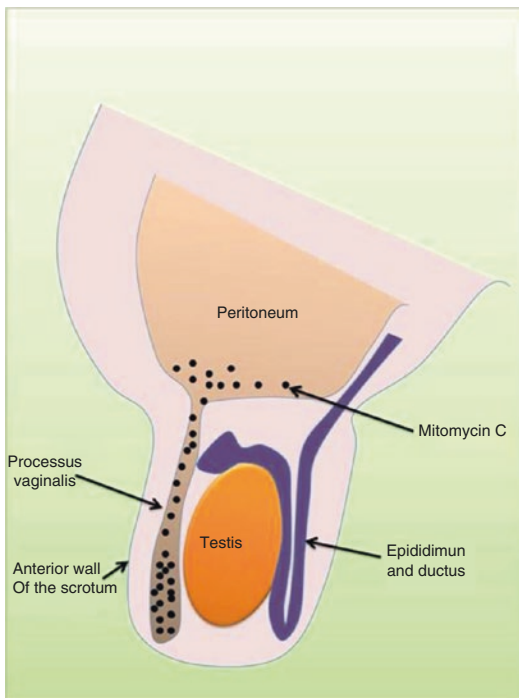
Fig. 26.33 Probable mechanism of mitomycin C deposition in a patent processus vaginalis into the scrotum

administration of mitomycin C inhibits wound healing and induces skin necrosis. (ii) Local spillage of mitomycin C onto the scrotal skin, with resulting inflammation and ulceration.

Previous studies with patients on continuous ambulatory peritoneal dialysis (CAPD) have shown that 10% of CAPD patients developed

genital swelling [3]. A possible cause of the scrotal swelling is a patent processus vaginalis causing a communicating hydrocele, which can be found in 15–37% of adult men and may not be clinically evident until CAPD has begun.

Patients may develop this complication months after the surgery; hence, any complaint of scrotal pain or discomfort in these patients should warrant immediate investigation and attention, even if the complaints present much later.

Our group suggests that an image investigation, such as computed tomographic peritoneography, should be considered for male patients prior to intraperitoneal chemotherapy, since this complication is potentially serious for the patient.

Vascular Conditions Associated with Chemotherapy [74]

Vasomotor Changes [74]

Various vascular alterations have been described, probably as a result of a direct effect on arterial smooth muscle fibers or by acting on the autonomic nervous system.

Manifestations may include blood vessel spasms with livedo, Raynaud's phenomenon, and distal necroses, which may be triggered by bleomycin and cisplatin. Vasodilatation with erythema and flushing may result from the use of bleomycin, cisplatin, asparaginase, dacarbazine, taxanes, 5-fluorouracil, doxorubicin, cyclophosphamide, gefitinib, and carmustine.

Flushing [74]

Flushing consists of a temporary erythema of the face, neck, upper chest, ears, or upper abdomen. The mechanism responsible for flushing is a transitory vasodilation mediated by the autonomic nervous system or by the direct effect of circulating substances that act on the musculature of the vessel walls.

The nerves of the autonomic nervous system also control the sweat glands so that flushing mediated by these nerves is known as "wet flushing," whereas when the substance acts directly on the vascular wall muscles it is known as "dry flushing." Derivatives of biological agents

such as L-asparaginase and bleomycin are notorious for causing flushing, which occurs soon after infusion. Irinotecan, a topoisomerase I inhibitor, causes dysautonomia, the symptoms of which include diarrhea, bradycardia, and flushing.

Hormonal agents such as antiestrogens (tamoxifen, anastrozole), LHRH analogs (leuprolide), and antiandrogens (flutamide and diethylstilbestrol) may result in flushing. Other agents that also deserve mention include 5-fluorouracil, carboplatin, cisplatin, cyclophosphamide, dacarbazine, doxorubicin, etoposide, and methotrexate.

Interactions with Radiation [74]

Interaction with UV Light [74]

Eruptions resulting from photosensitivity are caused by various agents, principally following exposure to UV radiation. Phototoxicity caused by dacarbazine, fluoropyrimidines (systemic 5-fluorouracil, topical 5-fluorouracil, tegafur, and capecitabine) and vinblastine has been well documented.

Phototoxicity caused by dactinomycin, doxorubicin, hydroxyurea, procarbazine, brequinar sodium, mitomycin, 6-thioguanine, and flutamide, as well as by the porphyrin compounds that are used in photodynamic therapy, is uncommon.

Reactivation of sunburn is a well-documented adverse effect following the use of methotrexate. It occurs when the drug is administered 1–3 days after exposure to UV radiation, when the erythema from the previous exposure has been in the process of disappearing. Leucovorin does not prevent this reaction.

Phototoxic reactions resemble intense sunburn in areas of the skin that are exposed to light, with erythema, edema, pain, or pruritus. Blisters may be present and desquamation may occur in severe cases. Residual hyperpigmentation may persist for months.

Hydroxyurea has been described as being associated with development of dermatomyositis-like eruption due to photosensitivity (Fig. 26.34) [74, 75].

Hydroxyurea is an anticancer agent that inhibits DNA synthesis through its action on the enzyme ribonucleotide reductase [75]. It is used in chronic myeloproliferative diseases such as polycythemia vera, chronic myeloid leukemia, and essential thrombocytosis, although it has also been prescribed to patients with refractory psoriasis [75]. Patients on long-term therapy with hydroxyurea can develop various side effects, including a wide variety of mucocutaneous manifestations, which appear in 10–35% of patients [75]. The most common skin changes are facial erythema, hyperpigmentation, xerosis, alopecia, skin atrophy, melanonychia, and ulcers on the

Fig. 26.34 Dermatomyositis-like eruption caused by hydroxyurea

Fig. 26.35 An aggressive squamous cell carcinoma on the ear of a patient under treatment with hydroxyurea

lower limbs [75]. Other less frequent adverse effects are dermatomyositis-like rash and non-melanoma skin cancer (Fig. 26.35) [75].

Dermatomyositis-like rash resembles true dermatomyositis both clinically and histologically [75]. It presents as desquamating erythematous papules or plaques on the dorsum of the hands, typically associated with facial erythema and pronounced xerosis of the skin. Patients rarely report other accompanying symptoms and there are usually no significant alterations of laboratory tests [75]. Histologically, a lichenoid inflammatory infiltrate is found at the dermoepidermal interface, with vacuolization of the basal layer, dyskeratosis, and, rarely, mucin deposition (Fig. 26.36) [75].

Diagnosis is made according to the distribution of the lesions and by the temporal relationship between chemotherapy and light exposure. Treatment includes discontinuation of the agent and protection from the sun for at least 2 weeks. Physical sunscreens are recommended. Cold compresses, systemic antihistamines, and topical or oral corticosteroids are used as associated symptomatic treatment.

Radiation Recall [74]

This is a phenomenon whereby the chemotherapeutic agent induces an inflammatory reaction in an area previously exposed to radiation. These reactions are predominantly cutaneous; however, they may affect internal organs such as the lungs, heart, bladder mucosa, esophagus, oral or bowel mucosa, and supraglottic larynx.

It occurs more often with the use of doxorubicin, dactinomycin, and gemcitabine and is less common with bleomycin, etoposide, hydroxyurea, methotrexate, trimetrexate, vinblastine, 5-fluorouracil, lomustine, daunorubicin, melphalan, cyclophosphamide, cytarabine, docetaxel, edatrexate, idarubicin, paclitaxel, tamoxifen, and vinblastine.

The mechanism of radiation recall is unknown but it is probably related to DNA repair. Relapsing dermatitis or radiation recall may occur between 8 and 15 days following radiotherapy and generally appears hours to days after administration of the chemotherapeutic agent.

Clinically, the patient may or may not experience a painful erythema with or without vesiculation, edema, desquamation, and pruritus. The borders of the lesion are well defined and correspond to the exact site at which the radiation was applied. In severe cases, necrosis and ulceration may occur.

The severity appears to directly reflect the brevity between radiation and chemotherapy as well as the doses of both radiation and chemotherapy. The reaction improves spontaneously within hours or weeks following cessation of chemotherapy, treatment being symptomatic.

The use of systemic corticosteroids associated with the discontinuation of chemotherapy generally results in a marked improvement and may permit reintroduction of the treatment.

Exacerbation of Radiation [74]

This occurs when a chemotherapeutic agent increases the toxicity of radiotherapy. This phenomenon may occur in virtually all the organs of the body including the skin, mucosa, esophagus,
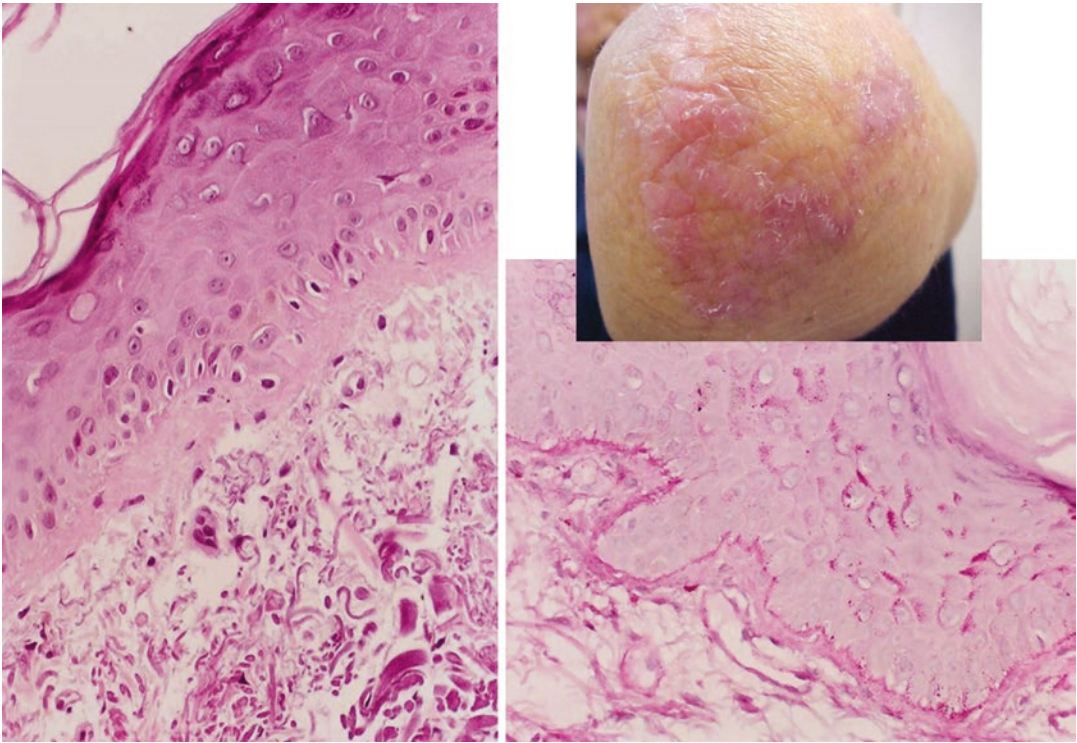
Fig. 26.36 Interface dermatitis on elbow of a patient under treatment with hydroxyurea

lungs, heart, digestive tract, kidneys, liver, brain, bladder, and eyes.

The agents most associated with exacerbation of radiation are bleomycin, gemcitabine, dactinomycin, doxorubicin, 5-fluorouracil, hydroxyurea, 6-mercaptopurine, oxaliplatin, and methotrexate.

Clinically, the reaction resembles residual dermatitis secondary to acute dermatitis from radiation, with erythema, edema, vesiculation, blisters, or erosions. The reaction generally appears at the site of radiation; however, the area affected may be more extensive. Severe mucositis may occur.

The reaction is associated with the dose, the type of drug used, and the sequence of time between radiation and the use of chemotherapy. Toxicity may be additive or supra-additive (synergic). In supra-additive toxicity, the reaction is greater than that of the sum of each one of the types of treatment alone.

Treatment is symptomatic: applying cold compresses, taking precautions at the site to prevent infection and avoiding trauma, heat, and UV light. Sequelae such as fibrosis, skin atrophy, and telangiectasia-related disorders may occur.

Hypersensitivity Reactions Caused by Chemotherapy Agents [74]

In theory, all chemotherapeutic agents may trigger hypersensitivity eruptions. With certain drugs derived from biological agents such as L-asparaginase, mitomycin C, and bleomycin in addition to paclitaxel, the incidence of hypersensitivity reactions is high. In the case of paclitaxel, this is due to the fact that it is dissolved in Cremophor EL castor oil.

According to the classification system defined by Gell and Coombs, the majority of hypersensitivity reactions are type I, i.e., IgE-mediated. They present as urticaria, pruritus, angioedema, and anaphylaxis. They generally occur within the first hour after use of the drug, but onset may be delayed until up to 24 h after using the medication.

Type III reactions occur because of formation of circulating immunocomplexes, and cause eruptions such as polymorphous erythema and vasculitis. Nonetheless, L-asparaginase and procarbazine cause urticarial reactions via type III reactions.

Allergic contact dermatitis, a type IV reaction, may occur, principally as a consequence of the topical use of nitrogen mustard (mechlorethamine).

Other severe reactions may occur, such as SJS and TEN, as well as exanthematous eruptions, all currently classified as type IV reactions according to the extended Gell and Coombs classification, i.e., SJS and TEN, respectively (type IVc, mediated by Fas, granzymes, and perforin) and exanthematous eruptions (type IVb, mediated by T cells with IL-5 production, with chemotaxis of eosinophils).

Local Reactions to Chemotherapy Agents [74]

Local Toxicity [74]

Antineoplastic drugs may be classified according to their potential aggressiveness toward blood vessels and adjacent tissues. They may be non-irritating, irritating, or vesicant, causing effects that range from mere local discomfort to tissue necrosis.

Nonirritating drugs (thioguanine, asparaginase, bleomycin, cyclophosphamide, chlorambucil, methotrexate, hydroxyurea) provoke an edema that is indicative of a site of extravasation; however, they do not cause necrosis or tissue irritation.

Irritating drugs (5-fluorouracil, carmustine, docetaxel, and etoposide) cause tissue damage that does not progress to necrosis. They trigger erythema, pain, inflammation at the puncture site and along the venous pathway, burning, and local edema, without blistering. The vesicant drugs (dactinomycin, doxorubicin, melphalan, vincristine, vinblastine, and dacarbazine) cause severe skin irritation with pain, erythema, edema, blistering, and necrosis with functional and aesthetic damage.

Drug Extravasation [74]

This is defined as the leakage of a chemotherapeutic drug from the vessel bed to the surrounding tissues, either as a result of vascular rupture or by direct infiltration.

The frequency of this event in adults is estimated at 0.1–6% and it is more common among children. Severe sequelae are rare. The severity of tissue damage is related to the type of chemotherapeutic agent used and the quantity and concentration of the drug administered.

Cytotoxic agents are classified as irritants or vesicants as a function of their potential for local toxicity. An irritant is defined as an agent that causes an inflammatory reaction, paresthesia, pain, or phlebitis at the puncture site or along the venous pathway.

Clinical signs include sclerosis and hyperchromia along the passage, as well as burning, increased temperature at the site, discomfort, erythema, and pain at the area of extravasation. Necrosis does not occur with this condition. The symptoms are generally short-lived and leave no sequelae. The drugs most associated with this complication are 5-fluorouracil, carboplatin, cisplatin, bleomycin, mitomycin, dactinomycin, idarubicin, daunorubicin, dacarbazine, ifosfamide, cyclophosphamide, mechlorethamine, carmustine, mitoxantrone, paclitaxel, docetaxel, streptozotocin, vinblastine, vinorelbine, and etoposide.

The vesicant agents (melphalan, bleomycin, mechlorethamine, carmustine, mitomycin, mitoxantrone, cisplatin, paclitaxel, dacarbazine, dactinomycin, daunorubicin, streptozotocin, doxorubicin, epirubicin, vinblastine, vincristine, etoposide, vindesine, and vinorelbine) have the potential to cause more severe and long-lasting tissue damage, including necrosis of the affected area.

The initial manifestations are often subclinical and may appear immediately following extravasation or after several days or weeks. The initial signs include local burning or paresthesia at the site of infusion, mild erythema, pruritus, and edema. A change in the infusion rate or the absence of venous return in the aspirate may

indicate the occurrence of extravasation. After 2–3 days, erythema increases and there is pain, a brownish discoloration, induration, dry desquamation, or the appearance of blisters. If the amount extravasated was small, the signs and symptoms may disappear in the following weeks. If a significant amount was extravasated, the following symptoms may appear in the coming weeks: necrosis, formation of eschar and painful, necrotic ulceration with raised, erythematous borders and a yellowish base. There is generally no granulation tissue with these ulcerations. They may resolve slowly or persist, increasing gradually in area. Involvement of the tendons, nerves, and vessels may occur if appropriate treatment is not given, leading to severe sequelae such as nerve compression syndrome, a reduction in joint mobility, contractures, neural deficits, and reflex sympathetic dystrophy. Cellulitis and the formation of abscesses are rare events.

The interval between detecting the condition and adopting the appropriate measures should be short as possible. The nursing team should be trained in this respect.

Preventive measures should be adopted such as avoiding puncturing emaciated limbs, lower limbs, limbs with multiple punctures, limbs with phlebitis or those that have been subjected to radiation, the ipsilateral limb to a mastectomy, in vena cava syndrome, and in veins that protect joints, nerves, and tendons. It is important to evaluate the venous conditions of the patient and, if necessary, to use an indwelling catheter.

The use of common needles for venous access should be avoided. Adequate fixation should be performed and blood reflux should be tested, with an infusion of 0.9% saline solution or 5% glucose-saline solution used for every 2 ml of the chemotherapeutic agent. After administration of all the drugs, 20 ml of saline or glucose-saline solution should be infused to reduce any possibly toxic residues.

Vesicant drugs should always be given first. In prolonged sessions of chemotherapy (those lasting over an hour) with vesicant drugs, central venous access should be used. Always listen to the patient's complaints. If extravasation occurs, stop the infusion immediately.

Remove the puncture device and elevate the affected limb. In the case of extravasation of drugs such as etoposide, paclitaxel, vinblastine, vincristine, and vinorelbine, apply local heat (leading to vasodilation and dilution of the drug) for 30 min and ice (venous constriction and greater degradation of the toxic metabolites in addition to alleviating pain and inflammation) every 30 min, six times a day in the first 48 h. For the other drugs, apply ice every 30 min, six times a day. When indicated, the specific antidote for the drug in question should be used.

The use of intralesional corticosteroid and sodium bicarbonate should be avoided. Ulcers that fail to heal may require debridement and grafting. In case of persistent edema and erythema and pain without ulceration that persists despite conservative therapy or in the presence of extensive areas of necrotic tissue or skin ulceration, surgery may be indicated.

Periorbital Edema [74]

Edema of the eyelids has been described with the use of gemcitabine.

Cutaneous Eruption of Lymphocyte Recovery [74]

Cutaneous eruption of lymphocyte recovery (ELR) is observed in leukemia patients who receive bone marrow ablation. In general, it appears between the 6th and 21st days after chemotherapy. This point corresponds to the beginning of the recovery of peripheral lymphocytes following the nadir of leukocyte count induced by chemotherapy.

Although the exact mechanism has yet to be clarified, it is believed that the eruption is caused by the return of immunocompetent lymphocytes to peripheral circulation with cutaneous cytotoxicity. T lymphocytes and Langerhans cells are found on histopathologic evaluation of these reaction sites.

Clinically, the condition consists of pruriginous, erythematous macules, papules, or papulous plaques that become confluent. Erythrodermia may occur. In addition, this

condition is associated with an elevation in body temperature that occurs together with the appearance of the eruption.

The temperature falls in the following 2–3 days and the skin eruption tends to diminish after several days, progressing with desquamation and mild residual hyperchromia. The drugs most associated with these reactions are cytarabine, daunorubicin, amsacrine, etoposide, cyclophosphamide, and vincristine.

Differential diagnosis should be made with sepsis, viral exanthems, GVDH, leukemia or lymphoma cutis, and drug hypersensitivity or toxicity. Histopathology is nonspecific. The most characteristic findings are superficial perivascular mononuclear cell infiltrate, mild epidermal alterations such as spongiosis, vacuolar alteration of the basal cell layer, and loss of keratinocyte maturation secondary to chemotherapy.

Dyskeratotic keratinocytes are rare and eosinophils are absent. On occasions when the patient was treated with GM-CSF associated with IL-3, atypical lymphocytes with large pleomorphic and hyperchromatic nuclei were found at histopathology.

Differentiation may be difficult between ELR and GVHD.

Skin Toxicity Associated with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors [74]

Anti-EGFRs currently consist of panitumumab, cetuximab, erlotinib, and gefitinib. Skin toxicity with anti-EGFRs is actually more of a pharmacologic effect than a hypersensitivity reaction, since this is a clinical marker of the efficacy of the inhibiting effect of these drugs on the tumor, with the severity of the eruption corresponding to tumor response.

The skin effects observed with the anti-EGFR are alterations in capillary growth and in the texture of the hair, paronychia with or without secondary infection, or the formation of pyogenic granuloma, generalized asteatosis, skin desquamation, and blepharitis.

The most characteristic and intense manifestation is a papulopustular, follicular, comedone, or non-comedo (acneiform eruption) that occurs on the head, neck, and the central portion of the chest and back, which later disseminates.

There may be pruritus, which differentiates this reaction from the acneiform eruptions caused by corticosteroids, antiepileptic drugs, and vitamins B6 and B12. Acneiform eruptions occur in more than 50% of patients with use of cetuximab, and this percentage may reach as high as 75–100%. The manifestations generally occur in the first weeks (2 days to 6 weeks) after the beginning of treatment (cetuximab and panitumumab).

The eruption is dose dependent; however, the duration of the condition does not correlate with the duration of treatment. The acneiform eruptions induced by monoclonal antibodies are more severe and extensive than those resulting from the use of tyrosine kinase inhibitors. Blepharitis caused by anti-EGFRs may range from mild to intense.

Histopathology of the papulopustular lesions shows no increase in sebaceous gland activity, comedones, or follicular rupture that would explain the inflammation, differentiating it from acne vulgaris. The follicles are rather wide and at times obstructed by an excess of keratinocytes. In the dermis, neutrophilic infiltrate may be found, particularly involving the follicular infundibulum. Intraepidermal acantholysis may be present in association with the eccrine gland ducts. In the lesions of patients using gefitinib, there is an expressive thinning of the stratum corneum layer with loss of the normal basket-weave pattern.

Paronychia occurs in around 10–15% of patients who are using cetuximab and gefitinib, appearing at 6–8 weeks of treatment or sometimes after 6 months. It affects various fingers and the first toes. Treatment consists of potent topical corticosteroids. In case of onychocryptosis, anti-EGFR may be temporarily interrupted and canthotomy performed. Asteatosis occurs in around 35% of patients, particularly with the use of gefitinib. There is a predilection for the areas previously or simultaneously affected by acneiform eruption.

Fig. 26.37 Intense xerosis caused by erlotinib

Some patients have xerosis of the vaginal mucosa, with dysuria. Xerosis may progress to chronic asteatotic eczema (Fig. 26.37), with a greater susceptibility to *Staphylococcus aureus* infection or HHV-1.

Emollients and topical corticosteroids should be used for the eczema. Fissures can be treated with a solution of 50% propylene glycol under plastic occlusion or a hydrocolloid dressing.

Glossary

Adverse drug reactions (ADRs)   Include all unintended pharmacologic effects of a drug except therapeutic failures, intentional overdosage, abuse of the drug, or errors in administration. They can be classified as predictable (type A – 80% of the ADRs) or unpredictable (type B).

Anaphylaxis   An immediate systemic reaction that occurs when a previously sensitized individual is re-exposed to an allergen. It is caused by rapid IgE-mediated immune release of vasoactive mediators from tissue mast cells and blood basophils with a potential late component. This is a systemic severe ADR affecting skin, mucous membranes, gastrointestinal tract, respiratory tract, and cardiovascular system.

Drug allergy   An immunologically mediated response to a pharmaceutical and/or formulation (excipient) agent in a previous sensitized patient.

Drug idiosyncrasy   An abnormal and unexpected effect that is unrelated to the intended pharmacologic action of a drug and has an unknown mechanism. It is not mediated by a humoral or cellular immune response but is reproducible on readministration. It may be due to underlying abnormalities of metabolism, excretion, or bioavailability.

Drug intolerance   An undesirable pharmacologic effect that may occur at low or conventional doses of the drug without underlying abnormalities of metabolism, excretion, or bioavailability of the drug. Humoral or cellular immune mechanisms are not thought to be involved, and a definitive mechanism for such exaggerated responses has not been established (e.g., acetylsalicylic acid-induced tinnitus at low doses).

Pseudoallergic (anaphylactoid) reactions   Immediate systemic reactions that mimic anaphylaxis but are caused by non–IgE-mediated release of mediators from mast cells and basophils. Often caused by radiocontrast agents.

Severe ADRs   Include all adverse effects which are unpredictable life-threatening ADRs and need prompt recognition to reduce integumentary and internal organ damage and, thus, morbidity and mortality.

Uncomplicated ADRs   Include mild or moderate adverse drug effects on healthy patients, not involving life-threatening situations.

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Part V

Dermatologic Diseases in Public Health: Environment and Skin Diseases

Cold and Heat

27

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Key Points Summary
- Skin is responsible for maintaining the body temperature and thermal balance
- Cold injuries are frequently associated with some degree of circulatory impairment
- Burns are the most prevalent heat injury; they are potentially serious and should be avoided
- In cold and heat diseases it is always recommended to evaluate the presence of an underlying disease

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Cold Injuries

Frostbite

Epidemiology

Frostbite is damage caused by the freezing of tissue upon exposure to extreme cold [1]. Several known risk factors are associated with this injury (Box 27.1), especially psychiatric problems, alcohol consumption, and drug use [2–4]. Alcohol and sedative drugs decrease the awareness of cold and impair the judgment necessary to warm up. Alcohol also inhibits shivering and causes cutaneous vasodilatation, predisposing to frostbite at warmer temperatures [2]. Typically, frostbite occurs when tissues are exposed to temperatures below the freezing point (typically −0.55 °C) for a period of time [5]. Frostbite most frequently affects the hands and feet (90% of reported injuries), but can also affect the face (nose, chin, ears, cheeks, and lips), buttocks/perineum, and penis [2, 3, 6].

Box 27.1 Risk factors for frostbite
General: prolonged exposure to cold, inadequate clothing, homelessness, smoking, dehydration, old age, high altitude.
  Systemic disease: diabetes, neuropathy, paraplegia, Raynaud's disease.

Mental illness or dementia.

Drugs: sedatives, β-blockers, and neuroleptics.

Intoxication: alcohol and illicit drugs.

Etiopathogenesis

In response to cold exposure, the body tries to preserve its temperature (vasoconstriction) and attempts to generate more heat energy (shivering) [2]. Cold injuries result from the limited capacity of the human body to cope with cold [6]. The effects result from direct and indirect freezing damage. Direct tissue injury occurs through the formation of intracellular and extracellular ice crystals. In the extracellular space, the ice crystals increase the oncotic pressure, dehydrating cells through outward diffusion of water and resulting in intracellular electrolyte disturbance [4]. The effects of damage to capillaries, microvascular occlusion, and progressive ischemia include generation of oxygen free radicals, production of prostaglandins and thromboxane A_2, release of proteolytic enzymes, and generalized inflammation [7, 8]. When the tissues rewarm, lysis of ice-containing cells and production of a prothrombotic microenvironment occur. Frostbite also causes less blood flow through localized vasoconstriction, an increase in viscosity, and microvascular damage through cooling of the vascular contents, which precipitates local transcapillary plasma loss and edema formation [4].

Clinical Presentation

Clinical manifestations of frostbite vary widely depending on the time since injury and the depth of injury [9]. The standard classification is divided into four degrees of injury. Clinically it is more useful to categorize frostbite as superficial (first and second degrees) or deep (third and fourth degrees) [6] (Box 27.2).

Box 27.2 Classification of cold injury
Superficial:
 1st degree.
 Partial skin freezing
 Erythema, edema, and hyperemia
 No blister or necrosis
 Occasional skin desquamation
 2nd degree.
 Full-thickness skin freezing
 Erythema, substantial edema
 Vesicles with clear fluid
 Blisters, desquamation, and black eschar formed
 Deep:
 3rd degree.
 Full-thickness skin and subcutaneous freezing
 Violaceous/hemorrhagic blisters
 Skin necrosis
 Blue-gray discoloration
 4th degree.
 Full-thickness skin, subcutaneous tissue, muscle, tendon, and bone freezing
 Little edema
 Initially mottled, deep red or cyanotic
 Eventually dry, black, and mummified

Most patients describe an initial feeling of cold, numbness, and sensory loss. The extremity will feel cold to the touch and patients often describe clumsiness and anesthesia, like "a block of wood" [3, 6]. It is often difficult to initially estimate the severity of frostbite injury, and there may be a wide discrepancy between the degree of damage to the skin and degree of damage to the deeper tissues [1]. The signs of good prognosis are normal skin color, blisters with clear fluid, and early formation of edema. Signs of poor prognosis are firm skin, lack of edema, nonblanching cyanosis, and small, proximal, dark hemorrhagic vesicles [6]. Physical examination helps to differentiate superficial from deep injury. Deep injuries are more frequently associated with blisters (clear or hemorrhagic). The most severe fourth-degree cold injury can present with a blue to gray skin color, with a hardened feeling to the skin on palpation [9].

Diagnosis

Diagnosis of frostbite is made clinically after a history of cold exposure. The patient describes a cold numbness with accompanying sensory loss.

The extremity will feel cold to the touch and may appear mottled blue, violacious, yellowish-white, or waxy [6].

Complementary Examinations

Technetium-99 bone scanning can be used to evaluate perfusion of bone and soft tissues. It has been shown to be useful at 2–3 weeks post injury to help clarify the extent of tissue loss [1, 2]. Angiography and magnetic resonance imaging may also help frostbite evaluation [5]. Plain radiographs are not helpful for early diagnosis, unless there is suspicion of concomitant fractures [1].

Differential Diagnosis

Chilblains is a benign condition related to a more chronic cold exposure characterized by pruritic, red-purple papules, macules, plaques, or nodules on the skin and often associated with edema or blistering, related to chronic vasculitis of the dermis. Trench foot is a nonfreezing injury caused by chronic exposure to wet conditions and temperatures just above freezing and is associated with arterial vasospasm and vasodilatation, with the affected tissue becoming cold and anesthetic, and then hyperemic after 24–48 h of exposure [8].

Therapeutic Approach

Firstly it is very important to treat life-threatening conditions before treating frostbite, especially if the patient is hypothermic. Next, frostbite should be treated with rapid rewarming by immersion in water at 37–39 °C, usually for 15–30 min. It is very important not to allow thawed tissue to refreeze, as it can lose its viability. If environmental conditions are such that thawed tissue could refreeze, it is safer to keep the affected part frozen until a thawed state can be maintained, especially if transport to medical care will take less than 2 h. Thawed areas should be air-dried rather than dried with a towel in order to avoid further skin damage [3, 10].

Most patients are dehydrated, and resuscitation with warm fluids is an important part of early management. Intravenous fluids should be warmed to 42 °C to prevent iatrogenic hypothermia [3, 8]. After rewarming, the treatment goals are to prevent further injury while awaiting the demarcation of irreversible tissue destruction. The injured extremities should be elevated to decrease edema. Tetanus prophylaxis should be given according to the usual protocol. Prophylactic antibiotics are seldom necessary and reserved only for identified infections [2, 3, 8]. Clear fluid-filled blisters should not be routinely debrided because they provide a biological dressing and protect underlying epithelialization; however, if the blister is tense and at high risk for rupture, it can be aspirated [8]. Hemorrhagic blisters should not be aspirated or debrided. Topical aloe vera (a thromboxane inhibitor), nonsteroidal anti-inflammatory agents (e.g., ibuprofen), or aspirin are usually applied to decrease production of prostaglandins and thromboxanes that can lead to vasoconstriction, dermal ischemia, and further tissue damage [10].

Patients with deep injuries at risk for amputation should be considered for thrombolytic treatment with tissue plasminogen activator (tPA) plus heparin within 24 h of thawing [3, 10, 11]. Contraindications for tPA use include concurrent trauma, neurologic impairment, recent surgery, or hemorrhage [1].

Iloprost is a prostacyclin analog with vasodilatory properties that may also affect platelet aggregation and, therefore, decrease microvascular occlusion. The intravenous form of the medication is not approved by the US Food and Drug Administration. Iloprost can be used when there is a history of trauma or when the exposure has occurred over the last 24 h, unlike tPA [5, 10].

Complete demarcation of tissue necrosis may take longer if performed after damage has occurred. As a general rule, amputation and surgical debridement are delayed for 2–3 months, unless infection with sepsis occurs [8, 10]. Angiography, technetium-99 bone scan, or magnetic resonance imaging may be used to evaluate the injury and guide additional therapy [3, 8, 10].

Acrocyanosis

Epidemiology

The incidence of acrocyanosis is not definitely known and probably is misdiagnosed. It is more prevalent in children and young adults (usually

younger than 30 years). There are risk factors associated with acrocyanosis including exposure to cold, outdoor occupations, and low body mass index [12]. Primary (idiopathic or essential) acrocyanosis is more common in women. Secondary acrocyanosis may be associated with other conditions such as the use of certain medications and malignancies [14] (Box 27.3).

> **Box 27.3 Causes associated with acrocyanosis**
> Hypoxemia
>   Acrocyanosis of infancy
>   Cold agglutinin disease
>   Cryoglobulinemia
>   Anticardiolipin antibodies
>   Medications
>   Toxins
>   Malignancies
>   Infections
>   Malnutrition
>   Spinal cord injuries
>   Inherited metabolic disorders
>   Palmoplantar keratoderma syndromes

Etiopathogenesis

The exact etiology of acrocyanosis is unknown. The pathophysiology involves a decreased basal flow through the acral cutaneous microcirculation. Peripheral arterial vasoconstriction, resulting from increased tone of the arterioles associated with secondary vasodilatation in capillary and postcapillary venules with consequent cyanosis, has been described [12, 13]. Changes in blood viscosity, decreased oxyhemoglobin, and increased platelet adhesiveness have been associated with this disease [13].

Clinical Presentation

Acrocyanosis is an uncommon condition characterized by persistent and symmetric erythrocyanotic discoloration of the hands, feet, and face, which is not preceded by paleness (Fig. 27.1) [15]. The nose, ears, lips, and nipples are also often affected. The disease is temperature dependent and generally worsens with cold exposure [14].

Fig. 27.1 Acrocyanosis (courtesy of Dermatology Service of UFCSPA)

Diagnosis

The diagnosis of acrocyanosis is made clinically through history and physical examination. It is important to be differentiated from other acrosyndromes and vaso-occlusive diseases.

Complementary Examinations

There is no specific examination for the diagnosis. Laboratory investigation and imaging studies are needed to investigate the etiology of secondary acrocyanosis if it is suspected.

Differential Diagnosis

Erythrocyanosis is characterized by a dusky cyanotic discoloration that occurs over areas with thick layer of subcutaneous fat (lower legs and thighs). Chilblains occur after cold exposure as burning, erythematous, or purplish swellings, especially on fingers and toes, nose, and ears. Other symptoms such as itching, burning, and pain are often present, in contrast to acrocyanosis. Raynaud's phenomenon is characterized by paroxysmal episodes of triphasic color change (white, red, and bluish discoloration) of fingers and toes caused by exposure to cold or emotional stress. In vaso-occlusive disease the pulse is usually low or absent, different from acrocyanosis. The acrocyanotic limb becomes pale when elevated, different from venous occlusion [12].

Therapeutic Approach

There is no standard or curative treatment for acrocyanosis. General supportive actions to keep

the skin warm are important to control the disease (gloves, slippers, avoidance of exposure to cold, no smoking). In severe cases, drugs such as α-adrenergic blocking agents (prazosin) and calcium channel blockers (nifedipine, diltiazem) can be used with variable results. Other options that can be beneficial include topically applied nicotinic acid derivatives and minoxidil. Sympathectomy is rarely indicated [12–14].

Chilblains

Epidemiology

The prevalence of chilblains (or perniosis) is not exactly known and is believed to be misdiagnosed. It is relatively common in European countries with damp, nonfreezing cold climates, in the northern regions of the United States, and in the southern regions of South America [16]. Women, children, and persons with low body mass index are most often affected [17].

Etiopathogenesis

The pathogenesis of idiopathic perniosis remains poorly understood. Some evidence suggests a disruption in the regulation of dermal blood flow, resulting in a challenge to thermal homeostasis [16]. In the majority of cases chilblains are idiopathic, but can be associated with some diseases [16, 18] (Box 27.4).

Fig. 27.2 Chilblains (perniosis) (courtesy of Dr. Francine Seibt)

hands, feet, and less frequently the face (nose, cheeks, earlobes) and legs (heels, shins, thighs, hips) (Fig. 27.2). Lesions are frequently associated with pain, pruritus, or burning. It can progress to blisters, erosions, ulcers, and permanent skin discoloration. Chilblains are induced by a cold, damp environment (humidity enhances air conductivity) in the late winter and early spring months [17, 19]. The lesions usually resolve slowly in 1–3 weeks, depending on the degree of trauma.

Box 27.4 Diseases associated with chilblains
Chronic myelomonocytic leukemia
  Systemic lupus erythematosus
  Behçet's disease
  Cryoglobulinemia
  Cryofibrinogenemia
  Cold agglutinin disease
  Raynaud's phenomenon
  Peripheral arterial occlusive disease
  Anorexia nervosa
  Obesity

Clinical Presentation

Chilblains is characterized by red-to-purple papular lesions involving the acral skin, especially

Diagnosis

Chilblains are diagnosed by clinical features associated with a history of prolonged exposure to moderate cold and damp conditions. A careful physical examination reveals the classic lesions described above.

Complementary Examinations

In suspect cases of associated signs of systemic disease, chronicity, or recurrence, laboratory tests

should be performed. These include a complete blood cell count, antinuclear antibody titer, serum chemical profile, serum protein electrophoresis, anti-double-stranded DNA, anti-Sm, anti-RNP, anti-SSA/Ro, anti-SSB/La, C3, C4, cryoglobulin, cryofibrinogen, and cold agglutinin analysis to rule out cryopathy or connective tissue disease [16, 19]. There are no characteristic histopathologic features that confirm the diagnosis, but biopsy of the affected area may exclude the presence of other disorders, although rarely needed.

Differential Diagnosis

The differential diagnosis of chilblains is broad, depending on the appearance and locations of lesions and the clinical history. Atheromatous embolization, thrombotic embolization, and peripheral artery disease can be associated with blue toes. Erythema nodosum, cold panniculitis, erythema induratum (Bazin's disease), and nodular vasculitis can be associated with erythematous, nodular, and ulcerative lesions. Leukocytoclastic vasculitis can be associated with palpable purpuric lesion. Raynaud's disease and acrocyanosis are vasospastic disorders that may coexist with perniosis. Lupus pernio or chilblain lupus is a disorder seen in patients with systemic lupus erythematosus (SLE). The endothelial damage imposed by the inflammatory reaction seen in SLE causes ischemic tissue changes and skin lesions similar to those seen in idiopathic perniosis [16].

Therapeutic Approach

First of all, it is important to explain to the patient the association of the disease with cold and damp conditions and encourage the use of adequate clothing (gloves, socks, hats, scarves, and proper shoes) to keep warm and seek shelter during cold-weather conditions. The patient needs to avoid any form of nicotine consumption because of its capacity of amplify the vasospastic responses to cold [16]. Nifedipine, a calcium channel blocker, has been shown to reduce the duration, severity, and recurrence of pernio lesions and symptoms. It is usually used at 20–60 mg daily [16, 20]. Side effects of nifedipine include flushing, headaches, dizziness, and occasional hypotension [19]. The treatment is usually continued while the weather is cold, even when the lesions are resolved, as a secondary prophylaxis, especially in patients with frequent recurrences. Commonly used topical corticosteroids are sometimes helpful. Other unproven treatments include topical vasodilators (such as nitroglycerin creams), heparin ointment, calcium preparations, intramuscular vitamin preparations, and sympathectomy [16].

Cold Urticaria

Epidemiology

The prevalence of cold urticaria is not well defined, and it is most commonly noted in young adults [21]. Women are affected twice as often as men [22]. The most common form is the idiopathic form in 96% of cases [23].

Etiopathogenesis

Most forms of cold urticaria are primarily acquired (idiopathic). Some cases can be secondarily acquired, and these are associated with underlying conditions such as malignancies, cryoglobulinemia, and infectious and autoimmune diseases. A familial form of cold urticaria, a rare autosomal dominant condition with onset at an early age, has also been described [21, 22, 24].

Clinical Presentation

Cold urticaria is a form of physical urticaria that occurs after cold exposure. It is characterized by the development of weal-and-flare type skin reactions and/or angioedema caused by release of histamine, leukotrienes, and other proinflammatory mast-cell mediators. Symptoms typically occur minutes after the skin is exposed to cold, air, liquids, or objects, and are usually limited to cold-exposed areas [22]. The greatest risk with cold urticaria is the development of a systemic reaction resulting in hemodynamic collapse during generalized cold exposure (e.g., swimming) [25].

Diagnosis

Diagnosis is clinical and is confirmed with cold stimulation tests, the ice cube test being the most

commonly used. An ice cube is placed in a plastic bag and applied to skin (usually forearm) usually for 5–20 min. A positive reaction is noted by the formation of a wheal during rewarming of the skin [21, 26]. Recently, a more accurate test has been described using a Peltier effect-based electronic device (Temp Test®; Emosystems, Berlin, Germany), which allows exposure of the skin to thermal elements with defined temperatures in a more controlled evaluation [22, 27].

Complementary Examinations

Laboratory tests are indicated to exclude major underlying diseases and identify possible associated causes. Investigation may include complete blood count, erythrocyte sedimentation rate, antinuclear antibodies titer, serology for syphilis, borreliosis, human immunodeficiency virus (HIV), Epstein–Barr virus, search for cryoglobulins, cold agglutinins, and cryofibrinogens [21, 28].

Differential Diagnosis

Cold erythema is a reaction to cold exposure with local pain and erythema but not urticaria. Ice cube testing is negative, merely producing pain and erythema. In cold panniculitis the lesions appear 1–3 days after cold exposure and subside spontaneously within 2 weeks. Application of an ice cube to the skin will result in an erythematous plaque 12–18 h later [24].

Therapeutic Approach

Avoidance of exposure to cold (including ice cream, cold beverages, and cold water) is the first step in the treatment and prevention. In patients with secondary cold urticaria, the underlying disease must be treated to resolve the skin symptoms. Antihistamines are considered first-line treatment for urticaria. Traditionally, first-generation antihistamines (e.g., chlorpheniramine, diphenhydramine, hydroxyzine) were used. Second-generation (e.g., cetirizine, loratadine, ebastine) and third-generation (e.g., desloratadine, fexofenadine, levocetirizine) antihistamines are effective and well-tolerated treatments with less sedation than first-generation antihistamines, and nowadays can be used as the first-line treatment for cold urticaria [29]. If the standard doses are not effective, increasing the dosage up to four-fold is recommend to better control the symptoms and treat the disease.

Cryoglobulinemia

Epidemiology

Cryoglobulinemia is a small-vessel vasculitis associated with the presence of circulating cryoglobulins. Cryoglobulins consist of immunoglobulins that precipitate at temperatures under 4 °C, and dissolve when heated at 37 °C [30]. Cryoglobulinemia affects mainly the skin, joints, peripheral nervous system, and kidneys. The prevalence and incidence of cryoglobulinemia are unknown, especially because of the heterogeneity in the etiology, clinical presentation, and geographic distribution. It appears to be more common in patients aged 45–65 years, and more frequent in women [31].

Etiopathogenesis

Cryoglobulinemia is classified into three types according to the immunochemical analysis. Type I cryoglobulinemia is characterized by single monoclonal immunoglobulins linked to a B-cell lymphoproliferative disorder. Type II cryoglobulinemia is characterized by polyclonal immunoglobulin G (IgG) with monoclonal IgM with rheumatoid factor activity. Type III cryoglobulinemia is characterized by polyclonal IgG and polyclonal IgM with rheumatoid factor activity. Types II and III are also referred to as mixed cryoglobulinemia [32]. This disease can occur secondarily to underlying autoimmune (e.g., Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis), infectious (e.g., hepatitis C virus (HCV), hepatitis B virus, HIV), and malignant process (e.g., multiple myeloma, Waldenström's macroglobulinemia, B-cell lymphoma, monoclonal gammopathy of unknown significance), but rarely there is no known cause (i.e., essential cryoglobulinemia) [30, 33]. HCV is the most common cause and is especially associated with type II mixed cryoglobulinemia [34, 35].

Clinical Presentation

The main clinical manifestations are due to hyperviscosity, vascular occlusion, and deposition of immune complexes. Most frequently affected sites are skin, nerves, kidney, and joints. Clinical features are variable, ranging from mild clinical symptoms (e.g., purpura and arthralgia) to fulminant life-threatening complications (e.g., glomerulonephritis, widespread vasculitis) [31]. Dermatologic features include palpable purpura, ulcers, Raynaud's phenomenon, and acrocyanosis (Fig. 27.3). Neurologic features include peripheral neuropathy, and most frequently distal symmetric sensorimotor polyneuropathy. The central nervous system is rarely involved. Renal features include hematuria, proteinuria, glomerulonephritis, and renal insufficiency. Renal involvement is associated with worse prognosis. Musculoskeletal features include symmetric arthralgia, with polyarticular involvement of metacarpophalangeal joints, shoulders, knees, and ankles the most common presentation. Other features are fatigue, malaise, abdominal pain, headaches, confusion, small airway disease and interstitial lung disease, blurry vision, and oronasal bleeding [31, 33, 36].

Diagnosis

Diagnosis is based on the detection of serum cryoglobulins in association with purpura, arthralgia, and weakness, and sometimes with renal or neurologic involvement. Cryoglobulins are evaluated by the detection of protein precipitates in the

Fig. 27.3 Cryoglobulinemia

patient's serum maintained at 4 °C for at least 7 days, which dissolve when heated at 37 °C [31].

Complementary Examinations

The presence of cryoglobulins is essential for diagnosing cryoglobulinemia [33]. Other laboratory abnormalities frequently seen are low C4 serum complement fraction, increased erythrocyte sedimentation rate, increased C-reactive protein level, presence of rheumatoid factor activity, and mild normochromic normocytic anemia [31, 33]. It is mandatory to evaluate for underlying diseases such as lymphoproliferative, autoimmune, and infectious disorders, especially HCV infection.

Differential Diagnosis

The differential diagnosis is made especially with other vasculopathies (thromboangiitis obliterans, Henoch-Schönlein purpura, leukocytoclastic vasculitis), hematologic diseases (protein C or S deficiency, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura), autoimmune diseases (lupus erythematosus, scleroderma, dermatomyositis, rheumatoid arthritis, antiphospholipid antibody syndrome), and drug-related reactions with Raynaud's phenomenon, livedo reticularis, and purpura [36].

Therapeutic Approach

Treatment of cryoglobulinemia should be based on the severity of clinical manifestations, etiopathogenic mechanisms involved, and the associated underlying disorders. In HCV-associated mixed cryoglobulinemia, antiviral therapy with pegylated interferon (IFN) plus ribavirin is indicated [31, 34]. Rituximab, an anti-CD20 monoclonal antibody, has been indicated for the treatment of HCV-positive mixed cryoglobulinemia with severe organ involvement and/or without an early viral response [34]. Type I cryoglobulinemia is life-threatening because of the severity of cutaneous and visceral involvement and the underlying malignant hemopathy. The treatment is based on polychemotherapy, but specific treatment including plasma exchange, rituximab, corticosteroids, bortezomib, and

lenalidomide may also be indicated depending on the severity of clinical manifestations and the underlying hematologic disorder. In patients with mild to moderate noninfectious mixed cryoglobulinemia, therapeutic management includes resting, avoidance of cold temperatures, nonsteroidal anti-inflammatory drugs, and colchicine. In cases of severe disease the treatment is based on corticosteroids, immunosuppressants, plasmapheresis, and rituximab [30, 31].

Cold Panniculitis

Epidemiology

Cold panniculitis is more frequent during infancy and childhood following exposure to severe cold. There is no gender difference in incidence in children, and it usually occurs on the cheeks and chin. In adults it usually appears in women associated with horseback riding, and usually occurs on the thighs [37].

Etiopathogenesis

Although the exact mechanism is unknown, the pathogenesis of cold panniculitis is postulated to be similar to that of subcutaneous fat necrosis of the newborn, with high concentration of saturated fatty acids in the subcutaneous fat of neonates alongside increased susceptibility to crystallization and necrosis under cold temperatures [38]. Subcutaneous fat in newborns is rich in saturated oils such as palmitic and stearic acids, which have a higher solidification point. The subcutaneous fat tends to become more unsaturated with aging, and the solidification temperature diminishes [37, 39]. In adults it is usually associated with female gender, obesity, smoking, and exposure to cold weather for long time.

Clinical Presentation

There are two main types of cold panniculitis. Haxthausen's disease or "popsicle panniculitis" affects infants exposed to severe cold and occurs 48–72 h after exposure, and presents as erythematous, firm, tender nodules on the cheeks and chin in infants and small children [39–41].

The term popsicle panniculitis is used when children develop cheek lesions after sucking on an ice cube or popsicle. Cold panniculitis in children has also been reported after ice therapy in supraventricular tachycardia. Equestrian cold panniculitis is characterized by erythematous, violaceous, tender plaques on the upper lateral aspects of the thighs in young women practitioners of horseback riding [39, 40]. Wearing tight clothing for long periods in cold weather, heavy smoking, and age under 35 years predispose to equestrian cold panniculitis [42].

Diagnosis

The diagnosis of cold panniculitis is made by obtaining a history of exposure of the skin to cold. The vast majority of cases do not need further investigation. If necessary, biopsy may be indicated.

Complementary Examinations

Cold panniculitis usually does not require complementary examinations unless the diagnosis is not clear. Biopsy specimens show a lobular panniculitis with a mixed inflammatory cell infiltrate, most prominent at the dermal-subcutaneous junction [38]. There are no specific laboratory tests for the diagnosis, and further evaluation is not necessary in clinically typical cases.

Differential Diagnosis

In some cases, a clear distinction between cold panniculitis and subcutaneous fat necrosis of the newborn is difficult, and a cutaneous biopsy may be considered. Other causes of subcutaneous fat necrosis, such as hypercalcemia, α_1-antitrypsin deficiency, post-steroid, trauma, frostbite, and facial cellulitis, must be considered. Sclerema neonatorum is another disease in response to cold, but tends to occur in sick neonates, beginning in the lower extremities and often fatal [43].

Therapeutic Approach

Cold panniculitis resolves spontaneously and usually does not require treatment. Patients usually recover within several weeks after cold exposure and require only symptomatic relief and slow rewarming [40, 44].

Heat Injuries

Burns

Epidemiology

Burn accidents rank fourth among all injuries, ranked behind vehicle accidents, falls, and violence [45]. Children are the most affected by burn injuries. Scalding (hot objects or liquids) accounts for 80% of burns in young children, and flame-related injuries are more common in patients older than 6 years. Another group at high risk of burn injury are the elderly [46]. Preventive measures may lower the incidence in burns, especially in children, and it is recommended to alert parents and the population in general. The annual all-injury mortality and age-adjusted death rates caused by burns are 55 and 48 per 100,000 persons, respectively. These numbers are around three- to five-fold higher in developing countries [47].

Etiopathogenesis

Burn injuries occur frequently after exposure to hot objects or liquids, flames caused by lighters, lighter fluid, firecrackers, alcohol, and gasoline. These injuries can cause skin lesions with different degrees of damage and extension. There is a local and systemic response to the damage depending on the degree of burn injury. Damage depends on the temperature of the thermal energy source and the duration of contact [48]. The local response is coagulation of tissue with progressive thrombosis of surrounding vessels after the injury. If the burn exceeds 20% of the patient's body surface, there is a systemic response. In this case, there is release of mediators with a secondary loss of capillary integrity and consequent fluid loss. The systemic response leads to a hypermetabolic state, increasing the physiologic cardiac output over the first 48 post-burn hours. The burn wounds than are colonized by bacteria, and different degrees of secondary injury develop depending on the depth and gravity of the burn [36, 48].

Clinical Presentation

Burns can be classified by depth [46, 48] (Box 27.5).

Box 27.5 Burn degrees
1. *Superficial (first-degree) burns* (Fig. 27.4)
   - Only the epidermis
   - Pink, dry, and painful
   - No risk for scarring
   - Heal in 5–10 days
2. *Superficial partial-thickness (superficial second-degree) burns* (Fig. 27.5)
   - All the epidermis and part of the underlying dermis
   - Clear blisters
   - Wet, erythematous, and edematous
   - Generally do not cause scarring
   - Heal within 2 weeks

Fig. 27.4 First-degree burn

Fig. 27.5 Second-degree burn

3. *Deep partial-thickness (deep second-degree) burns*
   - All the epidermis and deeper layers of the dermis (i.e., reticular dermis)
   - White
   - Scarring
   - Heal in 3 weeks or more
4. *Full-thickness (third-degree) burns*
   - Involve full thickness of the dermis
   - Leathery, dry, insensate, and waxy
   - Often require skin grafts
   - Scarring and contractures
5. *Fourth-degree burns*
   - Destroy all skin layers
   - Extend through the subcutaneous soft tissue to tendon or bone
   - Risk of limb loss

Diagnosis

The diagnosis of burn injury is made by obtaining a history of exposure to a heat source and by skin examination. It is essential to determine the depth and the extension of burn injury, because this will determine the initial steps of burn assessment and management. Burn size is determined by estimating the percentage of the patient's body surface area that is covered by partial-thickness and full-thickness burns. First-degree burns are not included in the estimation of burn size [46]. The "rule of nines" diagram is the most used to determine this percentage (Fig. 27.6).
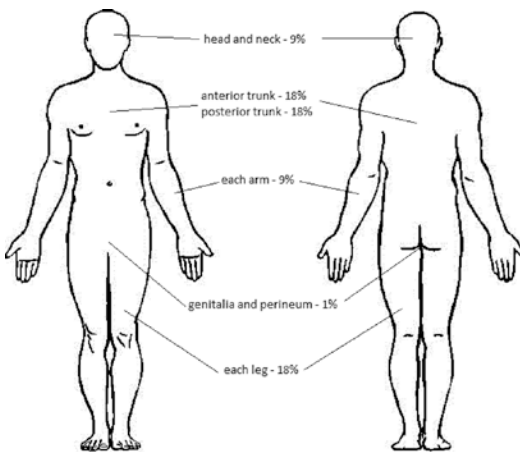
Fig. 27.6 "Rule of nines" diagram

Complementary Examinations

Burns usually do not require complementary examinations for the diagnosis. The most important evaluation concerns extent of the burn to determine the type of treatment the patient will need and the seriousness of the injury.

Differential Diagnosis

The differential diagnosis is directed to analyze clinical parameters and extent of burns to classify the degree of burn, the gravity, and the specific management necessary.

Therapeutic Approach

Most minor burns can be successfully managed in the outpatient setting. A tetanus shot is indicated for all patients with more than a first-degree burn. Cool running water after minor thermal burns is often used to reduce the depth of injury and increase re-epithelialization, but human studies are still limited in proving its effectiveness [46]. Management of blisters is controversial, but recommendations are usually to keep small (less than 6 mm) blisters intact [46]. Large blisters, blisters that prevent proper movement, and blisters that are likely to rupture can be drained. It is recommended to maintain the "ceiling" of the blister as a natural dressing. Some specialists recommend that the burn wound should be debrided before applying topical treatment. Many different kinds of topical treatments are used nowadays for partial-thickness burns. Topical antibiotics are frequently used to keep the wound moist, control pain, and slow bacterial growth. Silver sulfadiazine is one of the most worldwide topical treatments used because of its bactericidal activity that reduces inflammation and promotes healing [48]. However, there is limited evidence supporting improved mortality, wound infection, healing, or re-epithelialization rates in humans by silver sulfadiazine. Newer occlusive dressings can be used instead of silver sulfadiazine on the grounds that they result in faster healing, decreased pain, fewer dressing changes, and improved patient satisfaction. Some studies show that silver sulfadiazine has been consistently associated with poorer healing outcomes than biosynthetic (skin substitute) dressings,

silver-containing dressings, and silicon-coated dressings. Burns treated with hydrogel dressings appear to heal more quickly than those treated with usual care [49, 50]. Rare but serious side effects associated with silver sulfadiazine have been reported, such as agranulocytosis, leukopenia, Stevens–Johnson syndrome, anaphylaxis, toxic epidermal necrolysis, hemolytic anemia, hyperbilirubinemia, methemoglobinemia, and bacterial resistance [49]. Silver sulfadiazine is also relatively contraindicated in pregnant and lactating women, newborns, and patients with sulfa allergy [46]. Other topical treatments used are lotions, honey, and aloe vera. The lipid component of these products helps repair damaged skin and reduces drying. Honey has lately acquired a growing interest from the international scientific community and has demonstrated anti-infectious, anti-inflammatory, antiexudative, antioxidant, wound-healing, wound-debriding, and nutritional properties [51]. Topical corticosteroids are not recommended for the treatment of superficial thermal burns or sunburns as there is no evidence that they reduce the inflammatory reaction [46]. There is no scientific evidence that prophylactic systemic antibiotics improve mortality, so they are not recommended as a hospital management routine [46, 52]. According to the American Burn Association, referral to a burn center is indicated in patients with burns that involve the face, hands, feet, genitalia, perineum, or major joints; circumferential burns, because of the risk of compartment syndrome; partial-thickness burns on more than 10% of the total body surface area; and third-degree (full-thickness) burns in any age group [46]. Severe burn injuries create a hypermetabolic response that makes recovery difficult. Some treatments with anabolic agents, β-adrenergic receptor antagonists, and anti-hyperglycemic agents have successfully helped post-burn morbidities, especially catabolism, catecholamine-mediated response, and insulin resistance [45]. The most useful and studied drugs in these cases are propranolol, insulin, metformin, testosterone, and oxandrolone, recombinant human growth hormone, and insulin-like growth factor 1 (IGF-1) [45, 47, 53]. Treatment of severe burn injuries

also includes the biological skin substitutes that provide easier re-epithelialization recovery, especially because of the presence of a basement membrane. Cadaveric skin allograft, porcine skin xenograft, and amnion are the most widely used biological skin substitutes available in the burn centers, and are a helpful and inexpensive way to treat burns [54].

Erythema Ab Igne

Epidemiology

Erythema ab igne is seen more commonly in women and in patients who are overweight [55]. This skin disease is associated with chronic exposure to moderate heat, usually in people who sit in front of open fires, but also with the local use of hot water bottles, heating blankets, frequent hot bathing, heating pads, and, more recently, laptop computers [56].

Etiopathogenesis

The pathogenesis of this disease is poorly understood, but the radiation induces changes in dermal elastic fibers that are similar to those seen in actinic keratosis [57]. Heat exposure seen in erythema ab igne is presumed to induce damage to superficial blood vessels, leading to dilation and deposition of hemosiderin with the characteristic reticulate distribution [58].

Clinical Presentation

Erythema ab igne is characterized by reticular, erythematous, and hyperpigmented patches resulting from chronic exposure to external heat sources (Fig. 27.7) [55]. It is usually asymptomatic, but burning and itching can occur. Skin lesions are usually located on the shins and inner thighs when the patient sits close to fireplaces or heaters. It can be also located on the lumbar region and abdomen in patients who use heat sources [59]. There have been many case reports of laptop-induced lesions in recent years. In these cases the lesions are typically located on the thighs, especially on the left anterior thigh because of the location of the battery, optical drive, or heating elements of the laptop [57, 58].

Fig. 27.7 Erythema ab igne (Courtesy of Dr. Francine Seibt)

Diagnosis

The diagnosis of erythema ab igne is clinical, by obtaining a history of skin exposure to a heat source and presenting with the typical skin damage. If necessary, biopsy may be indicated.

Complementary Examinations

Biopsy usually shows variable features that are nonspecific. It can show increased epidermal atrophy, basal vacuolar changes, pigment incontinence, squamous cell atypia, dilation of post-capillary venules, and increased elastic tissue in the dermis [55]. Sometimes it could histologically resemble actinic keratosis, and chronic changes can lead to squamous cell carcinoma or, rarely, Merkel cell carcinoma [56].

Differential Diagnosis

The differential diagnosis of erythema ab igne includes poikiloderma, livedo reticularis, erythema dyschromicum perstans, vasculitis, and sun damage (actinic keratosis) [55, 60]. Graft-versus-host disease should also be considered as a differential diagnosis [59].

Therapeutic Approach

The first step in treatment is to discontinue use of the heat source. Early-stage lesions usually fade over months. Chronic lesions are more associated with hyperpigmentation that can persist for years. Treatment with topical 5-fluorouracil cream has shown good results when used for epithelial

atypia associated with erythema ab igne, which reflects histopathologic association with actinic damage [57]. Other treatments reported are topical tretinoin, corticosteroids, hydroquinone, and laser therapy [55, 59].

Glossary

Cellulitis A bacterial skin infection characterized by a swollen, red area of skin that feels hot and tender.

Chilblains Also known as pernio or perniosis, these are skin lesions resulting from abnormal response to cold temperature and characterized by erythematous or purplish lesions localized on fingers, toes, ears, and nose.

Cryoglobulins Immunoglobulins that precipitate in vitro at temperatures below 4 °C, and dissolve after rewarming at 37 °C.

Frostbite Defined by freezing, cold thermal injury, which occurs when tissues are exposed to temperatures below their freezing point for a sustained period of time.

Panniculitis An inflammation of the subcutaneous adipose tissue. Cold panniculitis is a form of traumatic panniculitis caused directly by cold exposure.

Raynaud phenomenon An intermittent ischemia of the fingers or toes characterized by severe pallor and often accompanied by paresthesia and pain, induced by cold and relieved by heat.

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Ultraviolet Radiation and Idiopathic Photodermatosis

28

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Key Points

- The solar spectrum band of interest for human beings contains UV-C (200–280 nm), UV-B (280–320 nm), and UV-A (320–400 nm) radiation
- Severe skin effects resulting from ultraviolet radiation can be divided into four categories: acquired idiopathic, photodermatoses from faulty DNA repair, photosensitization by exogenous or endogenous drugs or chemicals, and photoexacerbated dermatoses not directly resulting from UV radiation
- Solar polymorph eruption is regarded as the most prevalent idiopathic dermatosis, possibly reaching 20% of medical care for sun-related diseases in southern Scandinavia and 10% in the United States
- Actinic prurigo is more prevalent in females, with onset during childhood, frequently disappearing in adolescence; however, it may have lifelong persistence. Calcineurin inhibitors, such as tacrolimus and pimecrolimus, are used both for healing treatment and prophylaxis in specific cases
- In hydroa vacciniforme, a prevalence of 0.34 cases per 100,000 inhabitants is estimated, with similar onset when sexes are compared
- Chronic actinic dermatitis can develop in an absolutely normal skin, or in a body region previously displaying eczema, photoallergy, photosensitivity to drugs, or even solar polymorphic eruption
- The radiation spectrum which triggers solar urticaria shows variation depending on the geographic location and ethnicity, although its band ranges from UV-B to visible light

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Ultraviolet Radiation

Electromagnetic radiation (defined in Box 28.1) comprises waves or energy packages called photons and is part of a large variation of wavelengths from the high-energy X-ray (0.1–10 nm) to the low-energy radio wave (>10^6 nm) [1, 2].

The important radiation spectrum bands for human beings are untraviolet (UV)-C (200–280 nm), UV-B (280–320 nm), and UV-A (320–400 nm) (Fig. 28.1). When this energy enters the skin it is either dispersed or absorbed by some molecules (chromophores), possibly resulting in local biological reaction [1, 3]. It is important to note that the literature shows variations in the values of the spectrum bands of the ultraviolet radiation, both at the wavelength that divides UVC from UVB and from UVB with UVA. We use information from authors who reported the greatest wavelength difference between UVC and UVA.

Box 28.1 Ultraviolet radiation definition
UV radiation can be defined as the portion of the electromagnetic spectrum between the X-ray and the visible light band, that is, between 10 and 400 nm. It is worth noting the existence of vacuum UV radiation (10–200 nm), a band not present on the Earth's surface.

Being informed about the skin interaction with this radiation is crucial to understanding more than 100 known dermatologic diseases that have some dependence on solar exposure for their onset. This chapter focuses on a narrow band of the electromagnetic spectrum comprising UV radiation (200–400 nm) and visible light (400–760 nm). It is known that radiation with wavelengths less than 280 nm is absorbed by the stratospheric ozone layer and thus does not reach the Earth's surface. Long-wave UV, or UV-A (320–400 nm), on the other hand, is called black light, as it determines the emission of fluorescent brightness to some substances. About 95% of this UV radiation spectrum reaches the Earth's surface. UV-A is further divided into UV-A I (340–400 nm) and UV-A II (320–340 nm); the latter band has proved more harmful than the longer waves within this spectrum [1, 4].

Visible light (400–760 nm) is defined as the electromagnetic band with colors noticed by the retina. The short wavelengths are called the infrared (IR) band, which lies between 760 nm and 1 mm, and is subdivided into three bands: IV-A (760–1440 nm), IV-B (1440–3000), and IV-C (3000 nm – 1 mm). IV-A can penetrate the dermis, thus determining biological effects, whereas IV-B and IV-C are detected on the skin by a feeling of warmth [1, 4].

The UV-band electromagnetic radiation has many effects on the skin because of its action on the chromophores found in many skin layers. The direct action on the DNA leads to genetic mutations that may determine some skin cancers. Another mechanism for skin cancer development that also depends on UV rays is immune system impairment resulting from UV-B-induced action [5].

To deepen our understanding of the biological effects of UV radiation on the skin, we need to
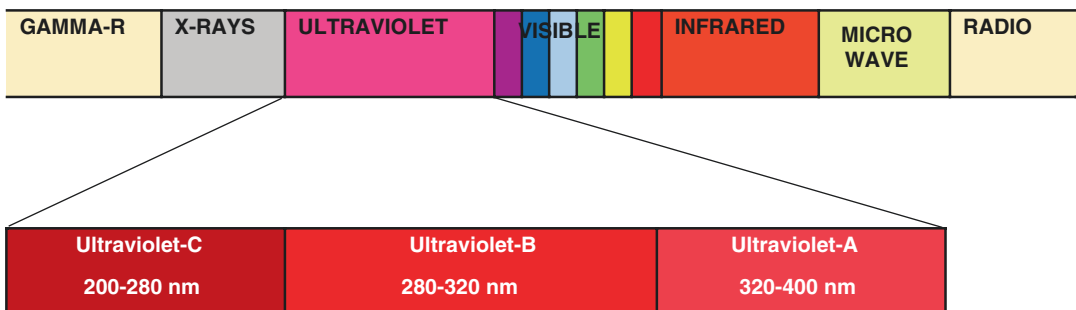
Fig. 28.1 Electromagnetic radiation bands

recall that its action is not limited to the effects on the keratinocyte DNA; it also changes some superficial molecules and induces the synthesis of immunomodulatory factors, including the interleukins (IL-1, IL-6, IL-8), tumor necrosis factor α (TNF-α), and prostaglandin E2 (PGE₂), among others. In addition, UV-B-irradiated keratinocytes bring about two potent immunosuppressant cytokines (IL-10 and TNF-α). IL-10 has as its main mechanism the inhibition of the ability of Langherans cells' to present antigens [5].

The skin exposed to UV radiation reacts with the epidermis directly after proliferation, mainly on the corneal layer but also on the dermal layer. Thus, hyperplasia occurs 24–48 h after this physical aggression. A light-skinned person exposed for 2 weeks, with suberythematogenic daily doses, shows a 20–40% increase in corneal layer thickness [5, 6].

Some research shows that this mechanism is the most important for protection of fair skin when it is exposed to UV rays [5]. Skin tanning is another defense used by the skin. UV-A exposure triggers a rapid pigmentary reaction with a transient change of the melanin already present in the skin through photo-oxidation, as well as melanosome redistribution, a process known as immediate pigment darkening. This process is followed by persistent pigment darkening, with stability for up to 2 h after UV-A exposure [5, 7].

Late pigmentation, known as melanogenesis, is a reaction to UV-B radiation, resulting from the increased amount and activity of melanocytes. This effect reaches its peak after a 10- to 30-day interval, depending on skin type and amount of radiation exposure. The activity of tyrosinase, a transmembrane glycoprotein in the melanocyte, determines the rhythm of the melanogenesis process [7].

Practically, melanogenesis aims at providing a reaction to the aggression on DNA, thus decreasing future damage resulting from UV radiation to this chromophore. A second mechanism used to help prevent skin cancer development is the individual ability related to DNA restoration mechanisms [5]. This protective arsenal includes the antioxidative mechanisms, various enzymatic and non-enzymatic processes that work to decrease oxidative damage. Superoxide dismutase, catalase, and thioredoxin reductase are examples of this protection system's enzymes. Besides these there are the natural antioxidants, such as vitamins A, C, E, and glutathione, responsible for the direct prevention of the development of O₂ radicals [5].

Although it still seems early to categorically state the role of vitamin D in cancer development, experimental studies have shown that vitamin D metabolites increase malignant cell apoptosis, inhibit angiogenesis and cell proliferation, and increase cell differentiation of the original tissues. Thus, they enhance the attenuation of skin cancer and improve the prognosis [8–12].

The severe skin effects resulting from UV radiation can be divided into four categories: acquired idiopathic (immunologically mediated photodermatoses, according to some authors), photodermatoses due to faulty DNA repair, photosensitization by drugs or endogenous and exogenous chemicals, and photoexacerbated dermatoses not directly caused by UV radiation [13, 14]. In this chapter the photodermatoses are described, which, although accepted by some authors as immunologically mediated, other authors still uphold the expression of idiopathic photodermatoses.

Idiopathic Photodermatosis

Polymorphic Light Eruption

Epidemiology

Polymorphic light eruption (PLE) is classified in the idiopathic photodermatoses, together with actinic prurigo, hydroa vacciniforme, solar urticaria, and actinic chronic dermatitis. Box 28.2 summarizes the main features of PLE. It is considered the most prevalent idiopathic dermatosis, responsible for up to 20% of medical appointments in southern Scandinavia, while in South Australia the prevalence is lower (5%) [13, 14]. It shows an incidence inversely proportional to geographic latitude [15]. Females are mostly affected, reaching 60% of the reported cases in some research studies [16]. Nearly 70% of cases occur before 30 years of age, and 11% after age 50 years [17].

Box 28.2 PLE: Essential features
- Polymorphic light eruption is the most prevalent disease in this group of diseases.
- It starts minutes after, or hours after sun exposure.
- The pathogenesis is suggestive of a hypersensitivity reaction to induced antigens, or antigens activated by ultraviolet radiation.
- The traditional cutaneous changes are described as papules and papular, erythematous, pruriginous lesions, or light-exposed skin plaques. They do not leave scars.

Etiopathogenesis

In general, the lesions start after sun exposure during early summer and in temperate climates. Experimentally, lesions can result from patients submitted to sources of UV-A, UV-B, and high-intensity visible light. The pathogenesis suggests that it is a hypersensitivity reaction to induced neoantigens, or activated by UV radiation [15]. After a 5-h submission to solar irradiation a prevalence of CD4$^+$ T lymphocytes are noted [14, 18]. However, 72 h later CD8 lymphocytes are largest in number, with Langerhans cells and dermal macrophages also showing increased amounts. These findings are very suggestive of a late hypersensitivity reaction.

Clinical Presentation

The dermatologic presentation develops a few minutes or hours after solar exposure (rarely, days). Other situations, such as sun reflections on the snow, or even artificial tanning beds, can also determine the presentation onset. Sometimes the possibility of onset decreases or is interrupted in sunny summers [13, 14].

Cutaneous changes have been described as papules (and papular), erythematous, pruriginous, vesicular lesions, or skin plaques exposed to light (Fig. 28.2). Scars do not develop. Other clinical presentations include hemorrhagic, erythema multiforme-like form, with an insect-bite

Fig. 28.2 Polymorphic light eruption

pattern, or strophulus-like form. In general, lesions are symmetrically organized (bilaterality) but irregular. When additional exposure to UV radiation is avoided, eruptions recede in hours or up to 2 weeks, leaving the skin completely normal. The sites mostly involved are the face, neck, upper anterior and posterior thorax, extensor portions of the upper limbs, and hands [14].

A phenomenon called induration, characterized by a decrease in clinical presentation features, even with ongoing solar exposure, may be observed in some cases, possibly determined by development of immunological tolerance thus showing a diminished clinical presentation.

Systemic symptoms, such as general malaise, cephalea, fever, and nausea, rarely emerge. The presentation has an episodic evolution over very long periods, possibly up to as long as 30 years [16].

Diagnosis

The diagnosis is made through analysis of the morphological characteristics of lesions, helped by the presence of more common symptoms, cutaneous location with prevalence in sun-exposed areas, and detailed history through reported relationship with sun exposure. Diagnosis is also helped by laboratory tests that enable preclusion of differential diagnoses, as well as compatibility with anatomopathologic findings.

Complementary Examinations

To rule out clinically similar diagnoses some tests can be important: for example, antinuclear factor (ANF); anti-Ro (SSA); anti-La (SSB); urinary, blood and stool porphyria levels; UV-A, UV-B, and visible light phototesting [14].

Histopathologic examination may help by revealing epidermal moderate acanthosis and spongiosis, and surface dermal edema. A histologic pattern may also be noticed with some dense dermal surface infiltrate and subepidermal edema, mainly in clinical lesions such as plaques. A compact perivascular lymphocytic dermal surface and deep infiltrate may be found. Direct immunofluorescence is common [16].

Studies revealed that in biopsy materials increased CD1$^+$ cell population was seen throughout the dermis of PLE patients. Current data suggest that this increase of the CD1$^+$ cell population represents the migrating of epidermal Langerhans cells to the regional lymphatic ganglia to display their antigen and trigger an IV-type immunologic response [16].

Differential Diagnosis

When considering the clinical characteristics, one must pay attention to history and physical examination details. Special attention must be paid to morphology, location, seasonal variation, evolutionary time, and lesion resolution following UV radiation.

Among the differential diagnoses, lupus erythematosus, reactions resulting from photosensitivity to drugs, photoaggravated dermatoses (atopical dermatitis and contact dermatitis), Jessner lymphocytic infiltrate, eczema, solar urticaria, erythropoietic protoporphyria, and sunburn can be included [16].

Therapeutics

Photoprotection is the most basic therapeutic measure. Good results may also be achieved with narrow-band UV-B phototherapy (UV-B NB) or psoralen photochemotherapy (PUVA) over 15 sessions at some time preceding the summer. This measure generally provides a favorable outcome lasting many months. For UV-B NB therapeutics (emission spectrum with a peak between 311 and 313 nm) an initial dose of 50–70% of the minimum erythematous dose (MED) is recommended, with increases of 10–15% at each treatment, applied two to three times a week. With PUVA, 0.5–0.6 mg/kg topical 8-methoxypsoralen is used, ingested 1 h before UV-A exposure. The UV-A irradiated dose varies from 0.5 to 3 J/cm^2, adjusted to the involved phototype. A systemic corticosteroid can be used in the first week, with an oral dose of 0.5–1 mg/kg body weight corresponding to that of prednisone. Achieving so-called skin induration may be tried through possible immunologic tolerance, with an indication of sun exposure of 15 min per day. Results with antimalarial drugs have not always been favorable, although some studies have shown a presentation improvement with hydroxychloroquine 400 mg/day. Ophthalmologic control every 6 months must be conducted as a function of the drug-related side effects [13, 14, 16]. Carotenoids at a dosage of 25 mg (10 mg of β-carotene + 15 mg of canthaxanthin) prescribed three times a day over the first month have shown good results. Carotenoid doses can be increased up to 150 mg/day (60 mg of β-carotene + 90 mg of canthaxanthin) in the second month [16].

Some studies have shown good results when using a substance called polypodium leucotomos, aimed at preventing PLE outbreaks, at doses varying from 720 mg/day (for individuals weighing less than 55 kg), 960 mg/day (individuals of 55–70 kg), and 1200 mg/day (for those >70 kg). This substance is extracted from a plant and has anti-inflammatory properties resulting from its strong antioxidant action, mainly due to the presence of polyphenols in its formula [15, 19].

Nicotinamide at a 1-g dose, three times a day (a total of 3 g/day), is also a good therapeutic option. Azathioprine (1.5–2.5 mg/kg/day) and cyclosporine (3.5–5 mg/kg/day) may be useful in cases of difficult management [13, 16].

Box 28.3 PLE Management
- Photoprotection is the most important basic measure
- Phototherapy with narrow band UV-B, or PUVA
- Systemic corticosteroid
- Carotenoids
- Polypodium leucotomos
- Nicotinamide
- Hydroxychloroquine

Actinic Prurigo

Epidemiology

Hutchinson prurigo, or hydroa aestivale, is a disease related to exposure to UV rays, described for the first time in 1879 by Hutchinson; this condition was renamed by Londoño in 1968 with the term actinic prurigo (AP) [13].

AP impairs all races and starts during childhood, with resolution many times occurring during adolescence, although it may be a lifelong condition. AP is common in native North Americans, mainly mixed race individuals of American Native or European origin, and individuals living in places of high altitude. It is also described in Europe and East Asia [13, 14].

A family history of PLE or AP may occur in up to 20% of cases. History of atopia is less common, occurring in 10% of persons with AP [14, 20].

Etiopathogenesis

UV radiation is the main determinant in AP lesions. In the spring and summer this disease displays a higher prevalence. The immunologic nature of AP may be found in a research study by Estrada et al. showing an excellent response to thalidomide as a function of the inhibited synthesis of TNF-α, and the CD3 modulation that produces interferon-γ [21].The presence of dense lymphocytic infiltrates and lymphoid follicles in biopsy samples of lesions also provides evidence to support the immunologic hypothesis [22].

AP may represent a clinically more persistent form of PLE, since the association between AP and PLE has been noticed in studies of specific families [23]. A noticeable association with HLA-DR4 (DRB1*0401) and the DRB1*0407 subtype has been seen either in United Kingdom patients and mixed-race patients, with the genetic factor possibly changing PLE into AP [20, 24].In fact, the presence of this subtype is powerfully suggestive of the diagnosis.

Clinical Presentation

AP is more prevalent in females and it has its onset in childhood, frequently disappearing in adolescence. However, it may maintain lifelong persistence.

The clinical presentation is characterized by papular and nodular lesions, sometimes with hemorrhagic crusts resulting from excoriations, mostly located on the face (including the nose) and limb extremities. The excoriations result from the characteristic pruritus symptom. Eventually, eczematous or lichenified presentations may be observed (Figs. 28.3 and 28.4). Distribution can be disseminated or dense, in areas with no sun protection, gradually evolving to reach the covered areas. Cheilitis and conjunctivitis may be noticed. Some superficial small linear hypopigmented scars may be seen on the face. Box 28.4 summarizes relevant AP features [14, 22].

> **Box 28.4 AP: Essential features**
> - More prevalent among females
> - More prevalent in spring and summer
> - Involving areas with no protection against the sun
> - Papular and nodular lesions, as well as excoriations and lichenifications
> - Cheilitis and conjunctivitis may occur

Diagnosis

The diagnosis is made through analysis of the morphologic characteristics of the lesions and presence of classic symptom of pruritus, its cutaneous location with a prevalence in areas of sun exposure, detailed history through reports of solar exposure, and laboratory tests as a support to rule out differential diagnoses, as well as compatibility with the anatomopathologic findings.

Complementary Examinations

Among the possibly requested tests, we may include antinuclear factor (ANFFAN), anti-Ro (SSA), anti-La (SSB), all useful to rule out lupus erythematosus. Laboratory typing or identification of the human leukocyte antigen (HLA), DRB1*0401 (DR4) type, or DRB1*0407, this second one mainly, can reinforce AP diagnosis [13, 14].

The anatomopathologic test displays the presence of moderate acanthosis, exocytosis,

Figs. 28.3 and 28.4 Actinic prurigo. (Courtesy of Dermatology Service of UFCSPA)

and spongiosis in the epidermis. On the dermis, the lymphohistiocytic infiltrate is moderate mainly in perivascular areas. Rarely the pathologist may find it difficult to make the differential diagnosis of lymphoma. In clinically persistent lesions nonspecific findings may occur, such as acanthosis, lichenification, and dense mononuclear infiltrate [14].

A phototest can confirm light sensitivity in 50% of cases, although it does not distinguish it from other photodermatoses [14].

Differential Diagnosis

Clinical differential diagnoses to be focused on include polymorphic solar eruption, lupus erythematosus, atopic eczema, seborrheic eczema, photoexacerbated atopic eczema, insect bites, nodular prurigo, and, very rarely, scabies [15].

Therapeutics

If a diagnosis was previously confirmed, prevention of development of the disease may be tried during a period before seasons when the disease develops more often through the prophylactic use of calcineurin inhibitors, such as tacrolimus and pimecrolimus.

Restricted sun exposure and use of a wide-spectrum and highly potent sunscreen may be advised, although their effect is limited.

Oral thalidomide at 50–100 mg at night, used intermittently, is almost always effective, even in resistant presentations [25]. However, possible side effects include somnolence, cephalea, constipation, and weight gain. Watchful control related to neuropathy development is an impor-

tant measure to be implemented. Owing to the high embryotoxicity with its well-defined effects, thalidomide is not approved in Brazil for this disease.

Oral corticosteroid in doses equivalent to prednisone at 0.5–1 mg/kg/day is very useful. Narrow-band UV-B phototherapy, or UV-A, chiefly after a corticosteroid is used for outbreak control, can be useful. In exceptional cases, azathioprine (a 1.5–2.5 mg/kg/day) and cyclosporine (3.5–5 mg/kg/day) are necessary.

Hydroa Vacciniforme

Epidemiology

Hydroa vacciniforme (HV) is a childhood disease first described in 1862. The Greek word *hydroa* means "watery eggs" as representation of a vesicular eruption. The word "vacciniforme," on the other hand, conveys the idea of "variola" pox-like scars that are left after blisters have healed [26, 27].

Estimates mention a prevalence of 0.34 cases for each 100,000 population, with the disease developing equally in both sexes. However, males show a higher impairment rate for HV when severe cases are considered, whereas milder cases are more prevalent among females. Familial cases are not common. In men the disease onset is late and the condition lasts longer. Distribution is bimodal, with peaks between 1–7 years and 12–16 years [27].

This chronic photodermatosis is rare, leads to scarring, and is characterized by groups of papu-

lar vesicles and vesicles, most often seen on the face and hand dorsum. It usually starts during childhood an lasts until puberty, when it shows a spontaneous relapsing trend. However, lifelong cases have been documented.

Some authors classify this disease as a scar presentation of PLE. Box 28.5 summarizes general concepts of HV.

Etiopathogenesis

The pathogenesis of this disorder is not yet well defined, although sunlight mainly in the UV-A band has shown great significance as a determinant factor when possible HV presentation with exposure to this radiation band is considered. The latent infection by the Epstein–Barr virus (EBV) has been referred to as an important factor in this association, since a high amount of DNA copies of EBV in the peripheral blood have been found as well as small codes of ribonucleic acid in cutaneous lesions. Cases of a large quantity of EBV copies are associated with patients with the worst prognosis [27, 28].

Clinical Presentation

The classic eruption starts in summer, with feelings of burning and twinges, and development of erythema possibly followed by local edema. Development of papules and vesicles then takes place, some of them displaying umbilication a few hours after sun exposure (Fig. 28.5). In a few

Fig. 28.5 Hydroa vacciniforme. (Courtesy of Dermatology Service of UFCSPA)

weeks pustules, crusts, and hypopigmented scars may develop. A larger number of lesions are seen on the cheeks, but also on other facial locations. The dorsum of hands and extensor aspects of the upper limbs may also show symmetric lesions. Oral ulcerations and eye changes are seldom although the can occur. Ophthalmologic complications, such as moderate photophobia, corneal ulcer, keratoconjunctivitis, uveitis, scleritis, and other manifestations can occur. Other sites are rarely affected [14, 27].

Complementary Examinations

It is important to rule out cutaneous porphyria from the diagnosis by requesting concentration of porphyria in blood, urine, and stool. Lupus erythematosus must also be considered and checked for with free α-amino acids (FAN) titration.

In the anatomopathologic test, spongiosis with development of intraepithelial vesicle spongiosis and keratinocyte necrosis will be found, associated with perivascular infiltrate of lymphocytes and neutrophils [14].

Differential Diagnosis

The differential diagnoses to be considered include herpes simplex, erythropoietic porphyria, polymorphic light eruption, subacute cutaneous lupus, and xeroderma pigmentosum [13].

Therapeutics

Therapeutic measures include restricted sun exposure and use of wide-spectrum and high-protection factor sunscreen. Sometimes antimalarials can be useful, although their routine administration is not well established. β-Carotene does not seem useful. Narrow-band UV-B phototherapy, or mainly UV-A, may be useful. Their application, nevertheless, must be careful and judicious to avoid exacerbation. Despite a low expectation regarding results, topical and/or systemic corticoids can be used, besides calcineurin inhibitors. Immunosuppressant drugs may be tried but are usually ineffective [13, 14, 27].

Chronic Actinic Dermatitis

Epidemiology

This condition is characterized as a rare chronic eczematous disease that usually affects middle-aged men, although it may also affect people older than 60 years. Some individuals present an atopic manifestation. The anatomopathologic test findings may sometimes be similar to those for pseudolymphomatous infiltrations. Persistent light reaction, actinic reticuloid, photosensitivity dermatitis, and photosensitive eczema are seen as clinical variants of chronic actinic dermatitis (CAD).

It is a disease diagnosed in many parts of the world, mainly in temperate areas. Box 28.6 shows its main features [13].

Etiopathogenesis

The pathogenesis of CAD is not yet well defined, but immunohistochemical and histologic studies have suggested a late hypersensitivity reaction even in the severe forms of pseudolymphomatous infiltration (so-called actinic reticuloid), whereby the same clinical and histologic characteristics are found in long-term contact dermatitis. Solar exposure as determinant of a reaction against photoinduced endogen antigens is suspected [14, 29, 30].

The necessary dose to trigger the clinical presentation is smaller than the necessary dose to determine a plain erythema. The presentation may be determined by exposure to UV-B and UV-A radiation, and even visible light. These are situations possibly indicating the existence of different photoallergens [14].

Therefore, there is a strong suspicion that CAD is a reaction similar to the one that occurs in allergic contact dermatitis, although against an altered DNA molecule by UV radiation or against another as yet identified molecule. There is also the possibility of increased immunologic reactivity due to a concomitant contact dermatitis resulting from an airborne material in individuals with prolonged exposure to allergens as well as and also UV radiation [14].

Clinical Presentation

CAD may develop in any normal skin or in a place where a presentation of eczema, photoallergy, drug photosensitivity, or even polymorphic light eruption was previously noticed. Concomitantly, a contact allergic process may be found, resulting from plants, airborne substances, perfumes, or even sunscreens. The condition worsens in summer and its onset is rapid after sun exposure. It is manifested through papules or erythematous plaques, dispersed or generalized; bright, infiltrated, pseudolymphomatous changes can be seen in severely affected individuals. The condition may display an acute, subacute, or chronic phase when showing plain lichenification. Pruritus is a characteristic. In sun-exposed areas there is a clear impairment compared with the non-exposed skin, with the areas protected by clothes clearly apparent. Lack of involvement of non-exposed areas can be noticed in skin grooves (wrinkles), upper eyelids, skin under ear lobes, and behind the ears. In severe cases, changes on the hand palms and foot soles can be identified. Eyebrows, eyelashes, and hair may fall out as a result of scratching (Fig. 28.6). There are rare cases of erythroderma in severe cases. Involution is estimated in 10% of the cases after 5 years, 20% after 10 years, and 50% after 15 years [13].

Complementary Examinations

As in most sun-associated diseases, it is important to rule out the hypothesis of subacute lupus and other forms of this disease. Thus, FAN titra-

Fig. 28.6 Chronic actinic dermatitis. (Courtesy of Dermatology Service of UFCSPA)

tion must be requested and, depending on the test result, anti-DNA, anti-Ro (SSA), and anti-La (SSB) must also be requested. With regard to lymphoma suspicion, care must be taken to interpret the presence of CD8+ Sézary cells because they can be present in CAD, even when a malignant disease is not present. Ruling out the presence of HIV virus as a predisposing virus is also important.

In the anatomopathologic examination, acanthosis and spongiosis with lymphocytic infiltration are found, usually limited to the upper dermis, with moderate cases displaying presentations of chronic eczema. More severe cases may histologically be similar to a cutaneous lymphoma of T cells, possibly resembling Pautrier's

epidermal microabscesses with a noticeable mononuclear infiltrate even with giant cells, but with no large quantities of mitoses [31].

The phototest may be crucial in confirming the diagnosis. Exposure to UV-B, UV-A, or visible light always shows reactions with erythema, eczema, or pseudolymphomatous aspects. The test must be applied to areas not routinely exposed to the sun when the diseased individual is not undergoing topical or systemic corticosteroid therapy [14].

Differential Diagnosis

The most frequent differential diagnoses include seborrheic eczema and atopical photoexacerbated eczema, photosensitivity reactions to drugs, T-cell lymphoma, and eczematous AP [13, 14].

Therapeutics

Treatment of CAD is difficult and displays limited reactions. Strict control of sun protection and exposure to contact sensitizers are key. High-potency corticosteroids, such as clobetasol propionate, provide noticeable symptomatic relief without local side effects, even when used for long periods. Systemic corticosteroids are also very useful in worsening outbreak phases. Calcineurin inhibitors, either tacrolimus and pimecrolimus, are also useful if well tolerated [13, 14].

For the less responsive cases to oral immunosuppressant therapy, azathioprine at 1.5–2.5 mg/kg/day usually leads to remission. In the winter the dose can be decreased or even suspended. Cyclosporine, 3.5–5 mg/kg/day, may also be useful. This choice generally provides a more effective outcome although with possible increased side effects. Mycophenolate mofetil is less useful in these cases, but if used is administered at a dose of 1–2 g/day. Phototherapy with low doses of UV-A, multiple

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Box 28.6 CAD: Essential features
- Chronic eczematous disease in middle-aged individuals and from 60 years of age on

- Characterized by papules or erythematous plaques, either dispersed or generalized, with bright, infiltrated, pseudolymphomatous alterations
- Potent topical corticosteroids, tacrolimus, pimecrolimus, and oral immunosuppressants can control the disease

times per week, may be useful in some cases, whereby concomitant control with topical and systemic corticosteroids is necessary to avoid exacerbation.

Solar Urticaria

Epidemiology

Some authors refer to solar urticaria (SU) as first being described in 1905 in a 47-year-old woman, whereas others propose that this name was suggested by Duke in 1923 when he reported a 43-year-old woman with a presentation of pruritus, erythema, and edema while being exposed to sunlight in a swimming pool [32]. In the literature there is a small prevalence of females in the fourth and fifth decades of life. SU possibly occurs worldwide at a rate of 3.1 in every 100,000 persons, comprising 1% of all forms of urticaria [14, 32].

Most diagnosed individuals can be permanently affected (68%) by radiation transmitted through glass (83%) and thin clothing (76%), as shown by Beattie et al. [33]

Etiopathogenesis

Like other forms of urticaria, the mastocytes have a significant function. Degranulation determinant factors are not well defined, although an immunoglobulin E (IgE)-mediated reaction against endogenous cutaneous or photoinduced circulating antigens is a possible mechanism, i.e., a type 1 hypersensitivity reaction. Two types of SU have been proposed, both resulting from the same action mechanism (IgE-mediated type 1 hypersensitivity). In type 1, the allergen would be generated only in SU patients, whereas in type 2 the allergen would be generated in both SU patients and normal individuals. Research studies have shown that the photoallergen molecular weights are different in each type, as are the electromagnetic radiation spectra [14].

There are reports of some medications inducing US development, such as some oral contraceptives, tetracyclines, and other drugs.

The spectrum of radioactive action that triggers SU is varied depending on the geographic location and ethnicity, but there is a band from UV-B to visible light. Nevertheless, Scottish research studies with a sample of 87 patients showed that 41% reacted to UV-A radiation and 30.9% to visible light only [27, 33].

In France, a research study reported that in 61 volunteers who had the disease, more than half of the cases resulted from UV-A exposure [34]. On the other hand, some studies complemented that statement by showing that more than half of the cases (63%) are triggered by two bands of electromagnetic radiation [33].

Clinical Presentation

The first outbreak usually happens after intense sun exposure or treatment with artificial tanning equipment. A classic presentation develops 5 or 10 min later, or, rarely, 20–30 min after exposure, with development of pruritus and erythema, followed by confluent urticarial plaques, with resolution in up to 1–2 h. Much less frequently, only pruritus may be noticed, starting many hours after sun exposure. When facing an extensive presentation, the patients may present cephalea, nausea, bronchospasm, and even syncope [33].

Lesions develop in all exposed areas with macular erythema, often followed by development of edema in the lesions, thus characterizing urticarial lesions. A demarcation can be seen between the exposed areas and those protected against radiation. Sometimes the face and the hand dorsum are spared because of tolerance to UV radiation (Figs. 28.7 and 28.8).

Very severe cases of SU can lead very rarely to fatal vascular collapse.

Fig. 28.7 Solar urticaria

Fig. 28.8 Elementary lesions of solar urticaria

Complementary Examinations

As previously described, in most sun-associated diseases it is important to rule out the hypothesis of clinical manifestation of lupus erythematosus. Therefore, tests such as FAN, anti-DNA, anti-Ro (SSA), and anti-La (SSB) must be requested. Blood, urine, and stool levels of porphyrins can rule out cutaneous porphyria [14].

Findings in the anatomopathologic examination include edema, dermal vasodilation, and neutrophilic and eosinophilic perivascular infiltration that develop a few minutes after UV exposure. Endothelial edema also shows early development. A large amount of eosinophilic granules are seen on the dermis 2–24 h after exposure, suggestive of eosinophilic degranulation [31].

Differential Diagnosis

Polymorphic light eruption, subacute lupus erythematosus (rarely coexisting with SU), seborrheic and atopical photoexacerbated eczema, erythropoietic protoporphyria (possibly secondarily causing SU), hepatic porphyria, and photosensitivity to drugs are significant differential clinical diagnoses [14].

Therapeutics

Strict rules for sun exposure associated with sunscreen use, as well as protective clothes, are useful measures to decrease UV-A exposure, although not enough for SU-inducing visible light. Dark clothes are more effective for protection than light-colored clothes.

The use of H1-antagonist antihistamines in higher doses than traditionally prescribed, ingested 1 h before exposure, is very useful in 30% of cases and partially effective in another 30% of cases.

In a case report cimetidine, an H2 receptor antagonist, led to a promising outcome [35].

Doxepin, an antagonist of H1 and H2 receptors, showed controlling effects with regard to this condition [36].

Phototherapy may be useful in patients who have developed sun-ray tolerance, although there is a need to maintain the therapeutics for long time; therefore, risks related to long-term use must be assessed. In addition, extra care must be taken to avoid anaphylaxis during treatment. The clinic where treatment occurs must be properly equipped so that risks for severe complication in this type of care can be minimized.

Oral cyclosporine at an oral dose of 4.5 mg/kg/day showed good results. Intravenous immunoglobulin can also be of use, with infusion doses of 1.4–2.5 g/kg from 2 to 5 days. The number of courses varies from one to three, with 2- to 9-month breaks. Remissions are sometimes reached 1 year later [27]. There are good reported outcomes with omalizumab, a recombined monoclonal anti-IgE antibody, at a dose of 150 mg every 2 weeks. This drug can be used for patients with high levels of IgE who have not obtained favorable results with other drugs [27]. Phototherapy, photochemotherapy, and intravenous immunoglobulin have been described as therapeutic alternatives that bring about good outcomes [27].

Box 28.7 SU: Essential features
- Small prevalence in females
- Larger prevalence in the fourth and fifth decades of life
- 3.1 in every 100,000 inhabitants
- Pruritus and erythema, followed by confluent urticarial plaques, with a resolution up to 1–2 h after solar exposure interruption
- In severe cases cephalea, nausea, and bronchospasm may develop
- Sun exposure restriction associated with use of sunscreen
- Doxepin, H1 antagonist antihistamines, phototherapy, cyclosporine**,** omalizumab

It is noteworthy that SU is a chronic disease requiring lengthy treatments with antihistamines or combinations. There are reported cases of spontaneous remission. Box 28.7 summarizes the essential features of this disease.

Glossary

Calcineurin inhibitors Suppress the immune system by preventing interleukin-2 production in T cells.

Catalase A common enzyme found in nearly all living organisms exposed to oxygen. It catalyzes the decomposition of hydrogen peroxide to water and oxygen.

Chromophores Molecules that absorb light. Visible light that hits the chromophore can thus be absorbed by exciting an electron from its ground state into an excited state.

Endothelin 1 A potent vasoconstrictor peptide originally isolated from endothelial cells.

Fluorescence The emission of light by a substance that has absorbed light or other electromagnetic radiation.

Human leukocyte antigen (HLA) A gene complex encoding the major histocompatibility complex (MHC) proteins in humans. These cell-surface proteins are responsible for the regulation of the immune system in humans.

Neoantigens Structures often associated with tumor antigens and found in oncogenic cells. Neoantigens can be formed when a protein undergoes further modification within a biochemical pathway such as glycosylation, phosphorylation, or proteolysis.

Phototest Specialized tests that confirm the presence of an abnormal sunburn reaction. This may occur when a photosensitivity is due to medications or chronic photosensitivity dermatitis.

Polyphenol A phytochemical antioxidant. It protects cells and body chemicals against damage caused by free radicals, reactive atoms that contribute to tissue damage in the body.

Psoralen The parent compound in a family of natural products known as furocoumarins, a class of phototoxic plant-derived compounds.

Superoxide dismutase An important enzyme with antioxidant action in almost all living cells exposed to oxygen.

Thioredoxin reductase A family of selenium-containing pyridine nucleotide-disulfide oxidoreductases. Thioredoxin reductase reduces oxidized thioredoxin in the presence of NADPH (nicotinamide adenine dinucleotide phosphate).

Wavelength The distance between identical points in the adjacent cycles of a waveform signal propagated in space or along a wire.

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Dermatoses by Plants

29

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Key Points Summary

- Although many affected individuals do not consult dermatologists, dermatosis by plants is a frequent and important source of contact among workers
- The main reactions are irritant contact dermatitis, phytophotodermatitis, contact urticaria, and allergic contact dermatitis
- The botanical identification of the contact plants is fundamental to performing specific investigations
- The main sensitizers are lactones, phenols, terpenes, aromatic alcohols and aldehydes, and usnic acid
- The most appropriate gloves and barrier creams for protection vary depending on the plant responsible

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Epidemiology

The frequency of skin reactions caused by plants is unknown since many affected individuals never consult their general practitioner and some reactions may be trivial and self-limiting or wrongly diagnosed. An exception is poison ivy/oak dermatitis in the United States, which is probably responsible for more cases of allergic contact dermatitis than all other provocations combined. Allergic contact dermatitis to poison oak and ivy is a major cause of occupational disability among workers, especially in the western United States [1, 2].

Gardeners, horticulturalists, agriculturalists, farmers, florists, foresters, and botanists all have frequent contact with plants. A large number of other occupations may also involve exposure to plants or plant products, such as sawyers, carpenters, wood machinists, antique restorers, builders, aromatherapists, herbalists, homeopaths, pharmacists, dentists, perfumers, beauticians, cosmetologists, food handlers, chefs, bar workers, military on exercises, and housewives. Some other activities may involve plant exposure, such as sports, especially golfing, fishing, cycling, rambling, hiking, mountain climbing, and camping. Romantics rolling in the hay and children at play are also at risk (phytophotodermatitis is common in children) [2].

Table 29.1 Cutaneous reactions to plants and plant products [2, 4]

Type		Etiopathogenesis	Onset	Duration	Characteristics
Irritant		Nonimmunologic	Minutes to hours	Hours to days	Polymorphous, restricted to areas of skin contact, itchy
Contact urticaria	Nonimmunologic	Toxin-mediated	Seconds to minutes	Minutes to hours	Urticaria, erythema, edema, pruritus
	Immunologic	IgE-mediated release vasoactive mediators such as histamine	Minutes to 1 h	Hours to 1 day	Urticaria, may be associated with atopy and worsen with subsequent exposure
Phytophotodermatitis		Nonimmunologic. Phototoxic	>8–48 h	Days to years	Caused by to psoralens, streaky, vesiculobullous, hyperpigmentation
Allergic contact dermatitis		Delayed-type hypersensitivity (type IV)	24–48 h	4–10 days	Polymorphous, itchy at areas of contact but may spread. Worsens with subsequent exposure

Etiopathogenesis

The major types of reactions resulting from plant contact are irritant contact dermatitis, phytophotodermatitis, contact urticaria, and allergic contact dermatitis (Tables 29.1 and 29.2).

Irritant contact dermatitis is not an immunologic reaction; it is caused by mechanical irritation such as macro- or microtraumas or chemical irritation from plants. Damage to the epidermal skin barrier occurs from contact irritants and subsequent activation of unspecific innate immune response, leading to inflammatory reactions [2, 3].

Phytophotodermatitis is mainly a phototoxic reaction that develops after contact with sensitizers on areas of bare skin that have been exposed to the sun [2].

Contact urticaria is an immediate response with immunologic and nonimmunologic mechanisms. When caused by nonprotein chemicals, it is most often due to nonimmunologic mechanisms. The immunologic type involves specific immunoglobulin E (IgE) synthesis, mainly to proteins, and can be severe with generalized or systemic symptoms, as observed in latex allergy [2, 3].

Allergic contact dermatitis is a type IV reaction or a cell-mediated hypersensitivity to antigens; prior contact with the allergen is necessary before the elicitation phase. Chemical allergens penetrate the skin and activate skin immune cells and skin structural cells. In particular the dendritic cells (DCs), such as Langerhans cells and different subsets of dermal DCs, become activated. These DCs then upregulate costimulatory molecules, migrate to the skin-draining lymph nodes, and present contact allergens in the context of major histocompatibility complex molecules in naive T cells, owing to a contact allergen–dependent polarization process. DCs secrete a combination of cytokines that polarize the T-cell response to Tc1/Th1 and Tc17/Th17 effector/memory cells. The inflammatory milieu is needed to overcome constitutive immune regulation. It removes the brakes on the immune system and enables a contact allergen–specific T-cell response. The priming of naive T cells seems to be paralleled by the induction and expansion of contact allergen–specific regulatory T cells (Tregs) that fail to prevent allergic contact dermatitis in the case of sufficiently strong allergens, but may prevent allergic contact dermatitis caused by weak contact allergens. In the elicitation phase, these Tregs help to downregulate the immune response. In their absence, the immune response is stronger and prolonged. The elicitation phase is initiated by repeated contact with the sensitizing contact allergen. The innate inflammatory response triggers the release of cytokines and T-cell-attracting chemokines. Endothelial cells are activated, and the contact allergen–specific T cells infiltrate the inflamed skin to exert their effector function [4].

Clinical Presentation

Irritant contact dermatitis starts minutes to hours after the contact and lasts hours to days. It has a polymorphous appearance, including dry skin, fissuring, pruritus, erythema, edema, vesicles, or necrosis. The lesions are usually restricted to areas of skin contact; however,

Table 29.2 Examples of dermatitic plants and plant products [2]

Types of plants	Irritant	Urticaria	Phytophotodermatitis	Allergic contact dermatitis
Garden plants	Borage, spurge, bulbs especially hyacinth	*Loasa, Iris, Tulipa*	*Dictamnus albus, Ammi majus, Ruta*	*Alstroemeria*, chrysanthemum, dahlia, feverfew, geranium, marigolds, bulbs especially *Narcissus*
Garden shrub/tree/climber	Thorns (rose), *Berberis, Pyracantha*	*Grevillea*		Gingko, grevillea, ivy, jasmine, Leyland cypress
Weeds	Ranunculus, *Euphorbia peplus*	Nettles (*Urtica*)	Cow parsley, cow parsnip, wild carrot	Dandelion, poison ivy/oak, yarrow
House plants	Cacti, croton	*Monstera deliciosa*		Chrysanthemum, orchid, *Primula obconica*, croton, ferns, *Philodendrum scandens*, *Euphorbia pulcherrima* Scheffler
Herbs	Borage, chives, comfrey		Parsley, rue	Anise, chamomiles, dill, lavender, mint
Countryside	Thorns (rose), tumbleweed, *Pulsatilla*	Nettles (*Urtica*), *Dendrocnide*	*Anthriscus, Heracleum, Angelica*	Ivy, lichens, liverworts, poison ivy/oak, ragweeds, *Helenium*
Ointment/cosmetics	Tea tree oil, apricot kernel, plant lipids (folliculitis), fragrances	Fragrances in toothpastes, henna, castor oil, cloves, sesame oil	Psoralens in essential oils and sun care products	Aromatherapy oils, ointments containing *Aloe, Arnica, Calendula*, fragrances, balsams of Peru
Occupational florists	*Codiaeum, Dieffenbachya*			*Alstroemeria*, chrysanthemum, ferns, orchids, *Primula obconica*
Food handlers	Garlic, onion, chives, peppers, lettuce, cereals, tomato plants	Lettuce, nuts, spices coffee, cereals	Celery, carrot, parsnip parsley, figs, citrus fruit	Asparagus shoot, carrot, cashew, chicory, citrus fruit, lettuce, mango, onion, peppers

glochids may cause an extensive pruritic eruption simulating scabies.

In phytophotodermatitis the reaction is typically erythematous, streaky, and vesicobullous, occurring within 8–48 h after contact with the plant. It appears precisely at sites of contact in sun-exposed areas and is associated with or followed by brown hyperpigmentation at the same site, which can persist for several weeks or months.

Nonimmunologic contact urticaria is a toxin-mediated reaction that provokes a reaction seconds to minutes after the contact. Erythema, edema, and pruritus last minutes to hours. On the other hand, immunologic contact urticaria starts within minutes to 1 h from the contact and lasts hours to 1 day, and may be associated with atopic patients. Vasoactive mediators are released, causing erythema, edema, and pruritus, which often worsen with subsequent exposure. In severe cases anaphylaxis may occur.

Allergic contact dermatitis often develops progressively within 1–3 days after exposure and lasts for 4–10 days. It is usually pruritic and streaky, with polymorphous appearance which may include erythema, vesicles, and edema. It starts at areas of contact but may spread outward. Recurrent episodes are typical, each lasting several days and usually followed by scaling. Each episode may be worse than the last. Minimal hyperpigmentation may occur. Airborne contact dermatitis typically affects the face, neck, forearms, and hands, simulating photosensitivity [2, 5] (Tables 29.1 and 29.2).

Irritant Contact Dermatitis

This is an inflammatory response to a physical and/or chemical injury and is not immunologically mediated. It depends on the barrier function of the individual's skin in addition to the potency and duration of the irritant stimulus. Therefore, mild irritants can cause a chronic cumulative dermatitis after repeated exposures. On the other hand, strong acids or alkalis from the sap of some plants may produce an acute toxic reaction with hemorrhagic bullae and necrosis [2, 3, 5].

Plants can irritate the skin by mechanical or chemical means. Although irritant contact dermatitis is very common, most patients do not seek a dermatologist because of the frequency of mild reactions. Its diagnosis is clinical and the patch testing is not recommended. Irritant plants often cause confusing patch test results and may even lead to chemical burns (Fig. 29.1 and Table 29.3).

Macrotraumas can be provoked by spines, prickles or thorns, and fall of branches or fruits. Leaves may act as knives. Such mechanical damage may lead to the development of infections.

In addition, microtraumas from trichomes or glochids (bristles or barbs) are also seen. These structures can penetrate the outer layer of the skin and cause papular irritant eruption, which sometimes mimic scabies, prurigo, or eruption similar to that caused by fiber glass. Some plants have stiff hairs that induce a stinging reaction, while others bear hooks or spines on their stems or fruits. Among these plants are species of *Cereus*, *Cephalocereus*, *Opuntia* as cactos-mandaracu (*Cereus jamacaru*), xiquexique (*Pilocereus gounelei*), and palms (*Opuntia vulvaris*) commonly found in northeastern Brazil. The implantation of cactus spines or hooks is an occupational hazard among pear pickers, and can cause a pruritic popular eruption called sabra dermatitis. Spine and glochids may also induce foreign body granulomata. Additionally they can introduce infective organisms such as *Clostridium tetani*, *Staphylococcus aureus*, *Sporothrix schenckii*, *Berberis*, numerous species of *Mycobacterium*, and actinomycosis [2, 3, 5–7].

Several plants contain chemical irritants and many possess irritant hairs or spines as well as chemicals. Chemical irritation is caused by either crystalline calcium oxalate, which has also a physical irritant effect, and a wide range of chemicals dissolved or suspended in latex or housed in specific organelles, including alkaloids, glycosides, proteolytic enzymes, saponins, phenolic compounds, and anthraquinones. Some members of the daisy family may produce an irritant reaction when crushed on the skin. Cactus-like plants contain a copious milky latex that is very caustic. Among them are the species of the Euphorbiaceae

Indian fig *(Opuntia fícus-indica)*

Agave

Borage

Euphorbiaceae

Dieffenbachia picta, the dumb cane
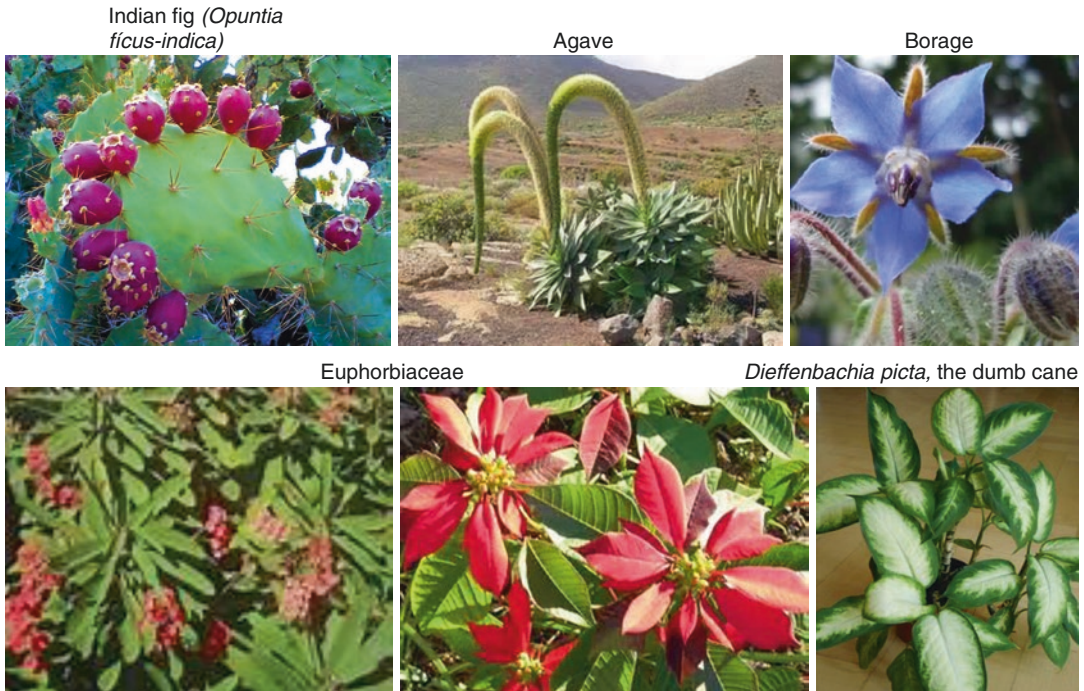
Fig. 29.1 Examples of irritant plants

Table 29.3 Irritant contact dermatitis [2]

Injury	Examples
Mechanical/physical	
Major traumas	Falling branches, fruits
Thorns	Roses (Rosaceae), bougainvillaea
Sharp-edged leaves and leaf hooks	Agave, *Yucca*
Spines and glochids	Cacti, *Opuntia*
Stem/leaf hairs	Borage, compositae (*Bidens*)
Irritant fibers	Rose hips, tulip bulbs
Chemical	
Stinging hairs	Urticaceae, Euphorbiaceae, Loasaceae, Hydrophyllaceae
Irritant sap/latex	Spurge (Euphorbiaceae), Ranuculaceae
Calcium oxalate crystals	Bulbs (Amarilidiaceae), Araceae, Bromeliaceae

family such *Euphorbia milli* (coroa-de-cristo), *Euphorbia pulcherrima* (bico-de-papagaio), *Euphorbia cyparissias* (erva-da-verruga), and *Euphorbia brasiliensis* (erva-de-leite), among others. Ingenol mebutate, the active agent (a macrocyclic diterpene ester) in the sap of the plant *Euphorbia peplus*, is used as a traditional remedy for several different skin lesions, including actinic keratosis and skin cancers. It provokes a severe skin reaction with erythema and blisters before the complete clearance of the actinic keratosis [8].

In the Araceae family, *Philodendrum* (costela-de-adão), *Monstera* (cara-de-cavalo), and *Dieffenbachia picta* (comigo-ninguém-pode) contain calcium oxalate. The last one is known as the dumb cane because it provokes edema, with blisters on the tongue and oral mucosa, leading to difficulty speaking. Plants of the mustard and radish family contain the glucoside sinigrin, which is harmless in the dry state but is converted to an irritant in the presence of water. Certain vegetables such as tropical gourds and cucumbers contain a juice that can irritate the skin. Pineapples contain bromelin, a proteolytic enzyme that is also an irritant [1–3, 5–7].

Acute irritant dermatitis can arise after some minutes or hours and include erythema, edema, papules, and vesicles, which are limited to the sites of contact. Chronic irritant contact dermatitis from plants, following repeated exposure to

the irritant, is commonly associated with xerosis, hyperkeratosis, and fissures. Patients may have more striking manifestations such as superficial necrosis, hemorrhagic blisters, and ulceration. The clinical picture may be further complicated by the presence of systemic findings, such as when the plant or plant product is consumed or inhaled [2, 3, 5].

Phytophotodermatitis

Phytophotodermatitis is a reaction caused by sun exposure after contact with plants. The reactions are phototoxic, owing to photosensitizing substances found in certain plants. An exception is the photoallergic contact dermatitis related to *Parthenium*. However, individuals exposed to volatile allergens such as Compositae oleoresin may become abnormally sensitive to light (persistent light reactivity).

Furocoumarins (psoralens) appear to be primarily responsible for phytophototoxic reactions in humans. Coumarin derivatives such as isopimpinellin also possess photosensitizing properties. They are seen in large amounts in citrus peel. Another category of photosensitizers are the furoquinolines [2, 3].

The most common plant families causing these reactions are Umbelliferae, Rutaceae, and Moraceae. Among them are parsnip, carrot, celery, lemon, lime, fennel, and parsley (Figs. 29.2 and 29.9). An interesting finding is that under attack by fungus, celery produces psoralen as a defensive mechanism [1, 2].

The eruption is related to areas of contact with the plant or plant product, followed by exposure to sunlight or an artificial UV-A light source. The distribution may be bizarre. Lesions develop 8–24 h after contact with these plants. They are linear dusky red lesions, often bullous and associated with brown pigmentation. During the summer in Brazil it is common to see young women who develop extensive and very severe bullous dermatitis after the use of home-made sun-tan fig lotions followed by sun exposure. Phototoxic contact dermatitis may present as berloque dermatitis, induced by perfumes or perfumed cos-

metics containing a high amount of psoralens, especially bergamot. In general it affects the neck or trunk. The hyperpigmentation that follows this eruption may last months or years, although it is now rare as such fragrances containing psoralens are no longer on the market. It can sometimes be observed with artisan or traditional fragrances [1–3, 9, 10].

A phototoxic reaction can follow the systemic ingestion of certain plants containing psoralen such as those from families Chenopodiaceae and Plantaginaceae. After eating, patients have to stay under the sun for at least 1 h. Massive edema and livid purple plaques, cyanosis and necrosis, vascular damage, hyperglycemia, and diabetes mellitus may develop [9]. In Brazil, the plant *Bidens pilosa*, known as "picão," is used in folk medicine for the treatment of jaundice and liver diseases. Consumed in topical preparations for baths as well as in teas for ingestion, it can develop phototoxic reactions due to phenyl heptatriene [6]. In Japan, phototoxicity was reported in patients who ingested a preparation containing an alga (*Chlorella* species) as a natural health food [2]. Furthermore, there are a few reports of phototoxic reaction to tobacco (*Nicotiana tabacum*) from cigarette smoke and snuff [11] (Fig. 29.2).

Contact Urticaria

The lesions are typical wheals that are short-lived (less than 24 h), associated with itch and tingling, limited at the site of contact and resolving without trace. Some plants may induce them by their pharmacologic mechanisms and others may provoke a type I hypersensitivity. The latter is caused by a plant-specific component, mainly proteins, and can be severe.

Nonimmunologic Contact Urticaria
Some species have sharp hairs on the surface of the leaves and stem. After contact they deliver a cocktail of irritant chemicals as a defense mechanism, provoking urticaria. Therefore, after puncture an irritant liquid containing several proinflammatory mediators, including histamine,

Case of phytophotodermatitis in a child due to lime contact   *Bidens pilosa*

Case of phototoxic   *Nicotiana tabacum L and Nicotiana*   Snuff
reaction due to snuff   *rustica L*

Fig. 29.2 Phytophototoxic reactions and photoirritants

acetylcholine, and 5-hydroxytryptamine is released into the skin. This reaction occurs at the site of contact and is immediate. The four main families with urticating hairs are Urticaceae, Loasaceae, Euphorbiaceae, and Hydrophyllaceae. Cansanção (*Cnidosculos urens*, *Fleurya aestuans*, *Loasa rupestris*), "favela" (*Cnidosculos phyllacantus*), "urtiga-cipó" or "urtiga-mamão" (*Dalechampia scandens*), "marmeleiros," "mucunã-brava," or "cabeluda" (*Mucuna urens*) are found in Brazil. Other plants with pharmacologic elicitors of urticaria are *Myroxylon pereirae* (balsam of Peru) and cinnamic acid derivatives therein contained, *Thapsia garganica* releasing thapsigargin, and species of capsicum with capsaicin [2, 3, 6].

Immunologic Contact Urticaria

Immunologic contact urticaria is an immediate type I contact reaction occurring in a previously sensitized individual. There is a specific IgE synthesis, mainly to proteins from a plant or plant product, which can cause a severe reaction with generalized or systemic symptoms. The reactions can occur with trivial symptoms such as itch, erythema, or wheals, or severe due to, for example, henna (*Lawsonia inermis*) in hair dye or celery.

Even fatal anaphylaxis to rubber latex has been described. It is commoner in atopics and individuals who have increased exposure to the allergen. The cutaneous reaction is at first at the site of contact, but the eruption can generalize. Cross-reactions can occur between botanically unrelated species.

Protein contact dermatitis is a reaction resulting from plant or plant products presenting as urticarial wheals or as an acute vesicular eczema at the site of contact, which is observed 30 min after exposure. It is mostly seen in persons with atopy who handle food, meat, or vegetables and have a previously chronic dermatitis (irritant or allergic) mainly on the hands and forearms. It has been frequently associated with food such as onion, lettuce, potato, carrot, or asparagus [2, 3].

The diagnosis is made by history and tests, among them which prick testing is indicated, using parts of a vegetable or commercial extracts with two readings: immediate and after 15–20 min. A scratch test may also be performed, but the former is safer and preferable. Serologic tests such as a radioallergosorbent test (RAST) to specific proteins can be used as an adjunct to skin testing or as an alternative when the prick test is contraindicated. The serum sample is assayed for

the presence of specific antibodies against the suspected substances. More recently the UNICAP system has also been used [2, 3].

Oral allergy syndrome (OAS) or pollen-food allergy syndrome is a hypersensitivity reaction to plant-based foods manifesting mainly on the lips, tongue, and mouth. The reaction occurs after prior sensitization to plant inhalant allergens. It is triggered by a cross-reaction between allergens in pollen and allergens in fresh fruits and vegetables. However, some plant allergens are resistant to heating, and patients may develop OAS after eating cooked food. Because digestive enzymes in the gastrointestinal tract break down the food allergens, the symptoms are typically limited to the oropharynx. It occurs in patients with a history of atopy. Systemic reactions rarely occur (Fig. 29.3).

OAS is a type 1 immediate hypersensitivity reaction, mediated by IgE induced by sensitization to pollen, which leads to subsequent development of cross-reactivity to food allergens.

The symptoms appear minutes after the exposure to the offending fruits or vegetables and last from minutes to hours. Reactions can develop from small doses of triggering allergen or in response to intimate or casual contact with someone who had consumed or handled the trigger. The symptoms are typically limited to the oropharynx and are usually mild and transient. Pruritus on the lips and palate region is common, although there may also be oral and perioral angioedema. Seldom extraoral symptoms include facial rash, nasal and otic pruritus, occasionally mucosal vesicles or blistering along the oral cavity, conjunctivitis, congestion, or coryza. On physical examination tongue swelling, uvular edema, erythema, swelling of the lips, perioral urticarial eruption, and facial edema (including the periorbital area) are apparent. Five percent of the patients have a generalized allergic reaction with systemic symptoms or even anaphylaxis. Risk factors for these reactions are a history of systemic reactions to food, a positive skin-prick test to commercial antigen, and prior reaction to peaches or tree nuts.

Many plants have developed proteins to protect against pathogen invasion. These are called pathogenesis-related or pathogen-response proteins (PR) and have been classified into 17 fami-
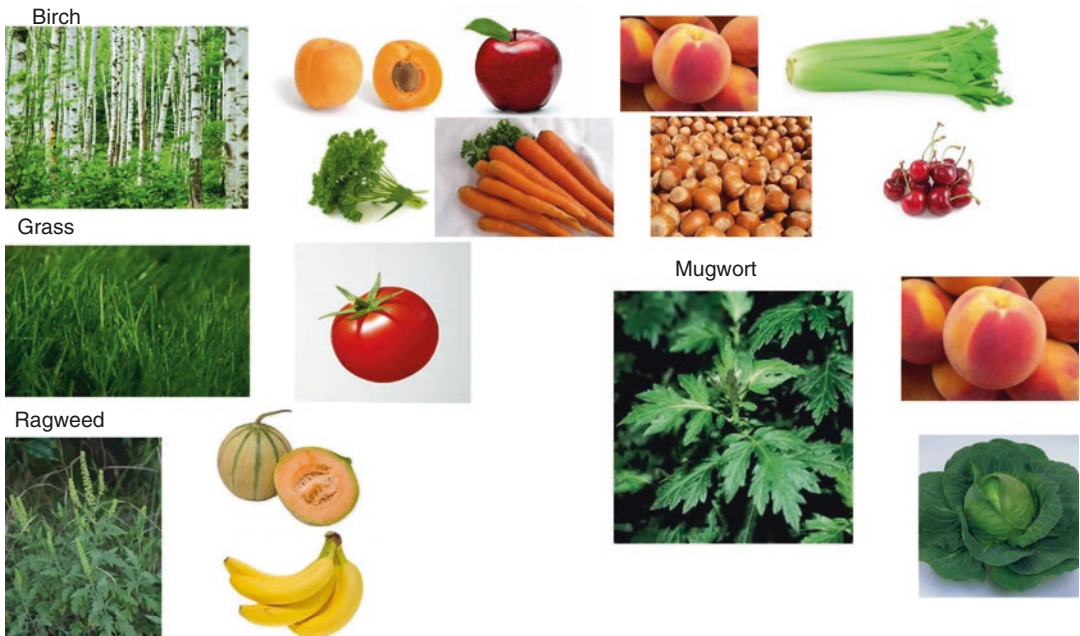
Fig. 29.3 Examples of inhalant allergens that cross-react with some fresh vegetable/fruit allergens provoking oral allergy syndrome

lies implicated in IgE cross-reactivity resulting in OAS. The PR-10 proteins are the most important family associated with pollen-allergy food. The major birch allergen Bet v1 is a member of this family, associated with hypersensitivity to various fruits and vegetables such as apple, cherry, apricot, pear, peach, hazelnut, celery, carrot, parsley, and potato [12].

Patients with atopic dermatitis who are sensitized to birch pollen may experience a worsening of their eczema after consumption of birch pollen-related foods.

The diagnosis is based on a history of oropharyngeal symptoms associated with ingestion of specific raw fruits or vegetables in patients with pollen allergies. Skin-prick testing with the suspected fresh food or with commercial extracts may be performed, the former being more reliable. Radioallergosorbent testing is more sensitive than skin-prick testing with commercial extracts but is less sensitive than skin-prick testing with fresh extracts. CAST-ELISA (cellular antigen stimulation test in combination with enzyme-linked immunosorbent assay) measures sulfidoleukotriene released by sensitized leukocytes after specific allergen stimulation. Although its utility in discriminating between sensitization and true allergy is questionable, it is useful to analyze cross-reactivity in patients with multiple sensitizations to plant foods and pollens.

The main treatment is the avoidance of known food triggers [12].

Allergic Contact Dermatitis

The isolation of specific chemicals that are plant sensitizers is a recent development in the study of the phytodermatitis. Most allergic plant dermatitis is due to a limited number of families and their sensitizers, closely related chemicals such as catechols and lactones. Therefore, the knowledge of these sensitizers is helpful for learning about this issue [1] (Table 29.4).

Tulipalin A (α-methylene γ-butyrolactone) is the main contact allergen in *Alstroemeria* and *Tulipa* species. It can develop tulip fingers, a painful dry fissured hyperkeratotic eczema on periun-

Table 29.4 Allergic contact dermatitis

Main plant sensitizers	Examples
Lactones	Tulipalin A (α-methylene γ-butyrolactone), sesquiterpene lactones
Oleoresin fraction (a mixture of substances: essential oils, terpenes, resins, phenols, and camphors)	Phenols: dihydric phenols, catechols (urushiol), resorcinols, hydroquinones
	Aromatic alcohols, aldehydes
	Terpenes: essential oils, balsams, resins
Usnic acid	Lichens (lichenized fungi): grow together with liverwort species such as *Frullania*

gual regions, fingers, and hands. Sometimes it spreads to the face, forearms, and genital area. The allergen penetrates vinyl but not nitrile gloves. A barrier cream containing cysteine may be protective [2, 3]. This hyperkeratotic eczema pattern on the fingers is also observed in allergic contact dermatitis cases due to diallyl disulfide, the principal allergen of garlic (Alliaceae family) [2, 3, 6, 7] (Figs. 29.4 and 29.5).

Sesquiterpene lactones are 15-carbon atom molecules in which a methylene group is attached to a lactone ring. Its antigenic portion is the α-methylene, which is bonded exocyclically to the γ-lactone ring. Over 1350 sesquiterpene lactones have been synthesized or extracted, and more than 50 are allergenic [2, 3].

The Family Compositae, comprising among others chrysanthemum and daisies, sunflower, chamomiles, feverfew, marigold (*Calendula*), herbaceous perennials (*Dahlia*), and vegetables (lettuce, chicory, and artichokes), is the main source of these sensitizers. However, sesquiterpene lactones are found in other genera such as *Frullania* (a liverwort), *Liriodendrum* (tulipa tree), and *Laurus nobilis* (sweet bay). A major allergen in airborne and occupational contact dermatitis from Compositae is parthenolide, which is the main sesquiterpene lactone in feverfew and tansy [1] (Fig. 29.6).

Although Compositae dermatitis can affect exposed surfaces as airborne dermatitis, it may mimic photodermatitis. However, hand dermatitis is more prevalent. Acute exudative flares occur during the growing season, but with
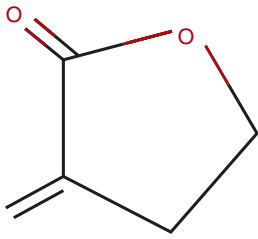
• Tulipalin A-
(Alfa-methylene-gamma-butyrolactone)

Fig. 29.4 α-Methylene-γ-butyrolactone
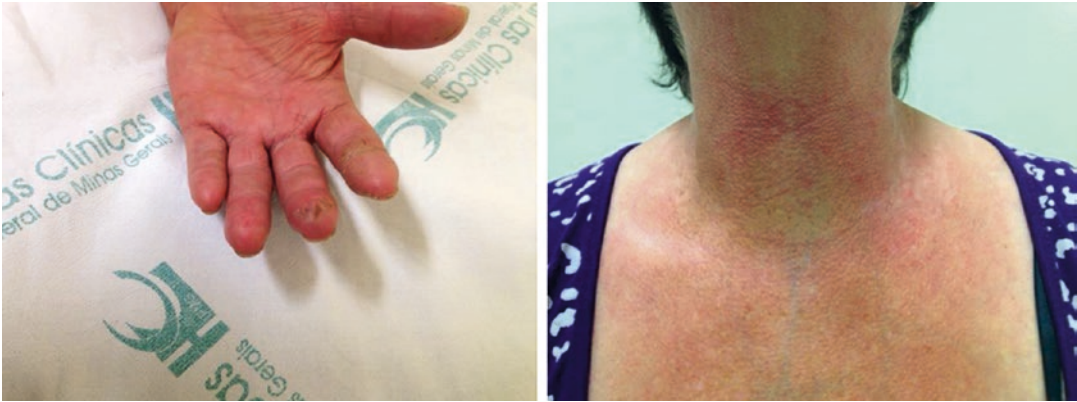
Fig. 29.5 Allergic contact dermatitis due to garlic in a food worker

• Sesquiterpene lactones
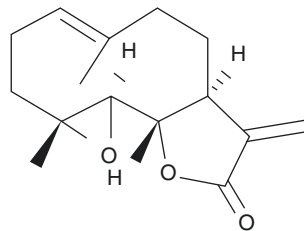
Parthenolide

Fig. 29.6 Sesquiterpene lactones

Fig. 29.7 Airborne allergic contact dermatitis to sesquiterpene lactone (Chrysanthemum) in a funeral service worker

repeated exposure chronic lichenified dermatitis is observed. Pollen dermatitis or ragweed oil dermatitis is a fairly common cause of Compositae dermatitis due to pollen grain, which contains the allergen, a resin-like material. The principal sites are the exposed areas suggesting an airborne pattern (Fig. 29.7). The typical seasonal appearance may be masked by chronification and secondary infection, which prolongs the duration beyond the pollen season. Oleoresin, an aqueous protein fraction in pollen can induce asthma, hay fever, and atopic dermatitis. Parthenium dermatitis due to *Parthenium hysterophorus* (feverfew, carrot weed) is a common manifestation seen in India where hundreds of cases of severe contact dermatitis are described (Box 29.1). Some may progress to a generalized erythroderma with fatal results. Besides the contact of the plants, other routes of sensitization or elicitation include ingestion (herbal teas) or the use of plant extracts in ointment or aromatherapy. Indirect contact via fomites may elicit dermatitis [2]. Bisabolol, a sesquiterpene alcohol, has been considered a potential cause of allergic contact dermatitis in children with atopic dermatitis and a history of intolerance to moisturizers containing this sensitizer [13].

Conditions in India proved to be favorable to its growth and the plant spread rapidly, becoming a major field weed. In addition, the plant grows much more vigorously in India than in America. It also contains large amounts of sesquiterpene lactone (parthenin), its main sensitizer, which is not seen in plants in South America. This is the first instance of an imported sensitizer causing allergic contact dermatitis [1, 2].

Although airborne Compositae dermatitis may be associated with photosensitivity, Compositae rarely cause photoallergy. Chronic actinic dermatitis has been described mainly in middle-aged to elderly men [2].

Patch testing for the Compositae family may include Compositae mix, sesquiterpene mix, and plant parts (pollen, stems, and leaves) or extracts [1, 2].

The sensitizing substances of many plants are present mostly in the oleoresin fraction and only in a few plants are the allergens water-soluble. The oleoresin fraction is responsible for the growth of the plant, making it more vigorous. It may be present throughout the plant and the pollen. This fraction consists of a mixture of substances including essential oils, terpenes, resins, phenols, and camphors. Of special interest are phenols (dihydric phenols, catechols, resorcinols, and hydroquinones), aromatic alcohols, aldehydes, and terpenes (Fig. 29.8).

The catechols and related compounds are important sensitizing substances in the Anacardiaceae family [1]. This family is an

Box 29.1
Parthenium hysterophorus (feverfew, carrot weed), an American weed, was introduced accidentally to India in 1956 in a consignment of wheat from the United States, causing allergic contact dermatitis in thousands of people, some of them fatal.

Aroeira, manga and cashew
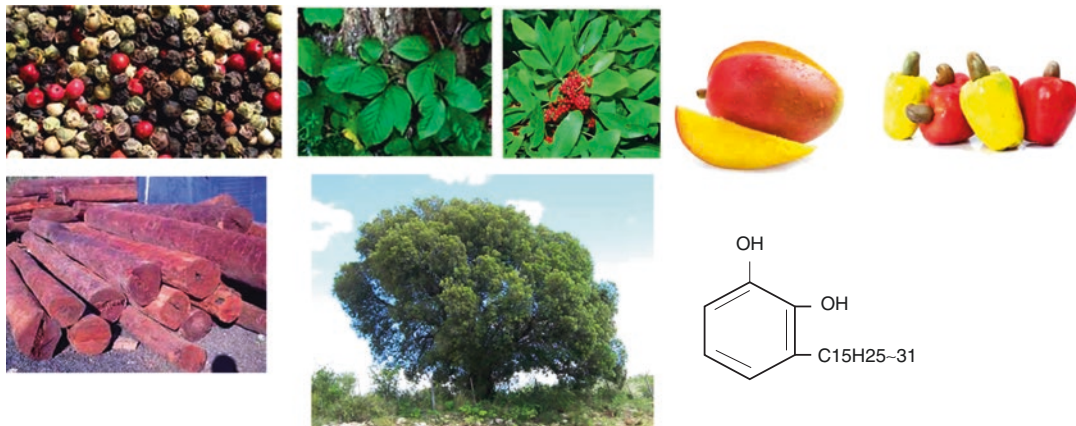
Fig. 29.8 Phenol sensitizers

important culprit and causes more dermatitis than all other plant families combined [3]. It includes the genus *Toxicodendron* (poison ivy, poison oak, poison sumac), which may cross-react to many species such as mango, cashew, Japanese lacquer, Indian marking nut, and African poison ivy [2]. The contact with leaves, bark, and sap from the leaves may cause sensitization to various alkyl or alkenyl catechols (urushiol), phenols, resorcinols, or salicylic acid derivatives. These compounds are also primary irritants [2]. Among them, urushiol, a mixture of pentadecylcatechols (PDC), is present in the oil of most members of the Anacardiaceae family and can elicit allergic contact dermatitis. Another compound, cardol, formed by resorcinol-type phenols that differ in their degree of unsaturation in the side chain of 15 carbon atoms, may cause similar reactions. A person sensitized to any one of the Anacardiaceae family plants will be contact sensitized to the others. The reason for this cross sensitivity is the common presence of phenols with the 15 carbon side chains (Table 29.5) [14], (Fig. 29.6) [6, 15].

Some sensitized individuals may react within hours of exposure with an extremely pruritic vesicular dermatitis. The majority develops a reaction 2–4 days after exposure. The first sensitizing dose, however, may not result in dermatitis for up to 3 weeks following the exposure [2]. The exposure may occur not only to the plant itself but also to contaminated fomites [2]. In general, the

Table 29.5 Some components of the Anacardiaceae family [1, 14]

Genus toxicondendron in North America and Asia	Other genus in South America (Brazil)
Toxicodendron radicans and *Toxicodendron rydbergii* (poison ivy)	*Anacardium occidentale* (cashew nut tree)
	Anacardium humile (caju-do-campo)
	Spondias lutea (cajá-mirim)
	Spondias purpurea (umbuzeiro)
Toxicodendron toxicarium and *Toxicodendron diversilobum* (poison oak)	*Mangifera indica* (manga)
	Schinopsis lorentzii (quebarcho-vermelho)
	Lithraea brasiliensis (aroeirinha-preta)
Toxicodendron vernix (poison sumac)	*Lithraea molleoides* (aroeira-branca, aroeirinha)
	Schinus molle (aroeira-do-Amazonas)
	Schinus weinmannifolius (aroeirinha-do-campo)
Toxicodendron vernicifluum (Japanese lacquer tree)	*Schinus terebinthifolius* (aroeira-vermelha)
	Schinus selloana (bálsamo-das-missões)
	Astronium urundeuva (aroeira-preta)

clinical picture is intense, especially if the resin is allowed to remain on the skin for a prolonged period. Washing the resin off may be effective if it occurs within a few minutes of contact. The face

and arms are often affected, but the lesions spread to the genitals and other parts. An airborne dermatitis may result from burning contaminated wood or brush. New lesions continue to develop in less heavily exposed areas days after the initial outbreak. The lesions may become secondarily infected and usually last 3 weeks [2]. One case of recurrent perioral dermatitis in a child sensitized to cashew apple, mango, and aroeira (*Astronium urundeuva*) is reported from Brazil, as well as cases of hand dermatitis and paronychia among cashew nut workers [16, 17]. Rash associated with *Astronium urundeuva* (alemão), a traditional medicinal plant in Brazil, is also reported [18]. Hyperpigmentation is a common complication in black skin, and in cases with antigen systemic absorption urticaria, erythema multiforme, or scarlatiform eruptions may occur. Allergic systemic contact dermatitis to oral or injected poison extract and immune complex disease affecting kidneys and skin are reported [1] (Figs. 29.9, 29.10, and 29.11).

Removing urushiol resin immediately after the exposure is important. Waiting longer than 10 min will almost certainly result in elicitation of the reaction among sensitized individuals. Contaminated clothes and fomites must be washed with detergents and organic solvents [2], but protecting clothes and gloves are important in prevention. On the other hand, quaternium 18-bentonite may reduce the percutaneous penetration of the urushiol and other cross-reacting agents. Ricinoleic acid (mamona oil) is also used for protection against cashew contact, especially among cashew nut workers [1, 16, 17]. As the catechols in urushiol are soluble in rubber, rubber gloves do not protect individuals from poison ivy. Heavy-duty vinyl gloves are indicated [1].

Substituted catechols include eugenol and vanillin, which are occasional sensitizers.

Primin, the major allergen of *Primula*, is a quinone (2-methoxy-6-n-pentyl-p-benzoquinone), which shows cross-sensitivity to other plants and woods that contain quinones. Another quinone allergen is lawsone (2-hydroxy-1,4-naphthoquinone), present in *Lawsonia inermis*. Henna, which is obtained from the plants' dried leaves, has been used as a red dye since ancient times. In Asia it is used to dye fingernails and in Western countries as a hair dye. Considering its

Fig. 29.9 Allergic contact dermatitis to aroeira

Lithraea molleoides

Fig. 29.10 Allergic contact dermatitis to aroeira (*Lithraea molleoides*) mimicking atopic dermatitis

Fig. 29.11 Aroeira products used in folk medicine such as teas, toilet soaps, creams, ointments, and elixir

widespread use the cutaneous reactions are very rare, and most cases are probably due to para-phenylenediamine, used in hair dyes (Figs. 29.12 and 29.13).

Terpenes are sensitizing agents in citrus fruits, celery, turpentine, chrysanthemum, and plant products such as resins and balsams. Many essential oils are terpenes, whose function in the life of the plant is not known. They may attract or repel insects or may be waste products of metabolism. The true terpenes are hydrocarbons and their alcohols, aldehydes, ketones, and other related compounds are also important. Among them are camphene, geraniol, citral, citronellol, linalool, myrcene, limonene, cineole, phellan-drene, menthone, menthol, α-pinene, camphor, and borneol.

Balsams are similar to resins but arise after injury to the plant. Resins can be phenolic deriv-atives or polymerization and oxidation products of terpenes.

Colophony (rosin) is the resin obtained from coniferous trees. There are three types depending on the method of extraction: gum rosin (the sap

Primula obconica *lawsone* - henna Primin

Fig. 29.12 Quinones: primin

Fig. 29.13 Allergic contact dermatitis due to paraphenylenediamine in henna tattoo

from living pine tree), wood rosin (extracted from pine stumps or wood), and tall oil rosin (a by-product of the pulp industry). Resin acids account for 90% of gum rosin and the remaining 10% are neutral matter. The resin acids are mainly abietic acid and its isomers neoabietic acid, palustric acid, and levopimaric acid. The main allergenic components in unmodified colophonium are oxidized resin acids formed by air exposure such as 15-hydroperoxyabietic acid and the oxidation products of dehydroabietic acid. Patients with positive reactions to colophonium usually also react to *Myroxylon pereirae* and perfume mix. Other cross-reactions are described with oil of turpentine, wood tar, pine resin, spruce resin, and tea tree oil. A case of allergic contact dermatitis to natural resin among gum rosin extractors is reported. Yet this case is rare, probably because natural rosin is less allergenic than the resin used in industrial products [1, 11] (Figs. 29.14 and 29.15).

The term balsam of Peru refers to a viscid fluid with an odor recalling cinnamon and vanilla. It is obtained from the wood of the tree *Myroxylon balsamum* after inflicting wounds on its bark. Two-thirds comprise the volatile oil cinnamein, which contains cinnamic acid, cinnamic aldehyde, cinnamic alcohol, methyl cinnamate, benzyl cinnamate, vanillin, and eugenol. The remaining one-third consists of polymers of esters of coniferyl alcohol with benzoic acid and cinnamic acid, the major allergens of balsam of Peru. It is found in a great number of products such as perfumes, food, spices, medicines, and beverages, and may show cross-reactions with cinnamon, clove, orange peel, rosin, and propolis [1] (Fig. 29.16).

Usnic acid is a relevant sensitizer that accumulates in lichenized fungi. Lichens are plants resulting from a symbiotic relationship between a fungus and an alga, and have caused

Fig. 29.14 Gum rosin extraction, resin sample, and positive patch test to resin in petrolatum 2%, 5%, 10%

allergic contact dermatitis in foresters. Usnic acid is chemically related to furocoumarins, but seems not to be a photosensitizer. It causes eczematous eruptions on the hand, face, and neck in wood cutters. Several species are used in perfumery [1, 2]. Cases of dermatitis in forest workers worsening during wet weather may represent multiple sensitization to usnic acid, lichen chemicals, and lactones [1]. Patch testing with lichens themselves may be misleading because many lichens grow together with liverwort species such as *Frullania*. On the other hand, patch testing with perfume mix, oak moss, atranorin, and usnic acid is recommended [2] (Fig. 29.17).
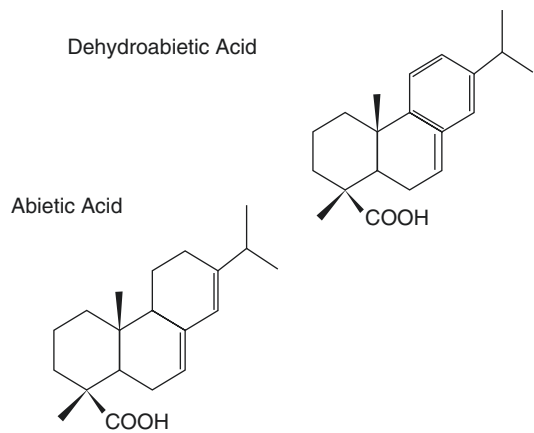
Fig. 29.15 Chemical structures found in rosin (colophony) and linked to allergy

Fig. 29.16 *Myroxylon balsamum*

Usnic acid
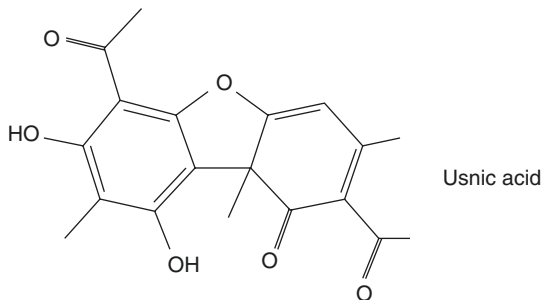
Fig. 29.17 Lichens

Woods

Although the incidence of wood dermatitis is small its study is important, especially in occupational area. Woods can cause allergic and irritant dermatitis, often with an airborne pattern. Contact urticaria and photocontact dermatitis are rare. The main sensitizers are benzo-, naphtho-, furano-, and phenanthrene quinones, stilbenes, phenolic compounds, and terpenes. The chemical substances responsible for the nonallergic reactions are alkaloids, glycosides, anthraquinones, saponins, phenols, and flavonoids [19].

Most dermatitis from contact with woods is occupational and affects carpenters, joiners, cabinet-workers, and forest workers. The last ones can be irritated or sensitized by the wood itself or by lichens and *Frullania* (a liverwort) that grow on the bark of the trees. Dermatitis from the solid wood of finished articles is less

common and has followed prolonged contact. It is related to the contact with musical instruments, bracelets, knives, and wooden toilet seats, whose popularity is increasing again [1, 3, 20].

Sawdust and fragments of wood can cause contact dermatitis affecting the hands, forearms, face, neck, and skin folds in which dust accumulates. These folds may be axillae, waist-band, groin, and ankles. These areas can be prone to irritant and allergic contact dermatitis [1]. Erythema multiforme-like eruption from Brazilian rosewood is reported. The inhalation of sawdust can cause asthma, inflammations of the oral mucosae and the respiratory system, carcinomas, and systemic symptoms if the wood contains pharmacologically active constituents.

The most highly sensitizing woods are of tropical origin, some of them containing quinones. Among them are Australian blackwood, Australian silk oak, Brazilian rosewood or palissander, cocobolo, grapia (Brazilian wood), incense cedar, pao ferro or caviuna vermelha, sucupira, teak, primrose, mahogany, and others. Other sensitizers include resins, terpenes, oils, phenols, formic acid and nitrogen-containing substances, and salicyl alcohol. Cross-sensitization is commonly described among them. Tulip poplar (*Liriodendron tulipifera*), *Magnolia* species, and bay laurel trees (*Laurus nobilis*) contain sesquiterpene lactones. *Frullania* species or liverworts are a group of nonvascular plants that grow on bark and rocks and have sesquiterpene lactones [1, 3, 21].

Fig and rubber trees, belonging to the *Ficus* genus, contain a milky sap called latex. Fig tree latex may cause allergic dermatitis and photodermatitis, while rubber latex rarely sensitizes [1].

Eucalyptus pollen is related to IgE-mediated contact urticaria without systemic symptoms. Eucalyptus oil has been found to be allergenic as well as tea tree oil, which contains 98.5% eucalyptol. Tea tree oil comes from *Melaleuca alternifolia* [1].

The pines (family Pinaceae) are rarely implicated in allergic contact dermatitis. However, patients with such dermatitis have positive reactions to colophony or turpentine oil, which are well-known sensitizers [3].

Tree pollen has an oil resin portion and an aqueous protein portion. The former may produce allergic contact dermatitis and the latter rhinitis and asthma. Beekeepers may have allergic contact dermatitis from the bee glue (propolis) derived from poplar and other resins. Patients allergic to propolis show cross-sensitivity to balsam of Peru [1, 2].

The diagnosis is based on the patient's history and occupation, the clinical aspect of the dermatitis, the botanical nature of the wood, and patch testing. The patch test must be with dry and then damp sawdust, since the damp one may release formic acid and other irritants. The best approach is to patch-test with freshly ground sawdust 10% in petrolatum and then to test controls. Botanical identification of the suspected wood is essential, so a solid wood sample (not wood dust) should be available for botanical identification [1, 19].

The prevention of contact dermatitis caused by woods is difficult. Ventilation to control the dust is important, as is the use of protective clothes. Since cross-reactions may occur, the substitution of species may not be a solution [19].

Essential Oils

Essential oils are used for medical purposes as alternative medicine. Their use combines massage with their application on the skin and is called aromatherapy. Nowadays there is a growing trend in the use of natural remedies worldwide, despite there being is no evidence-based therapeutic foundation [22].

The essential oils can be applied with massage, inhaled through vaporization, or used orally in the form of drops or honey. In the past they were also employed in fragrances, but nowadays synthetic chemicals are used instead. Therefore, aromatherapy is their main use at present. Most essential oils are of herbal origin. They can be extracted from plants and flowers by distillation, extraction, enfleurage, maceration, and expression. Essential oils are complex mixtures of compounds which may have over 100 constituents. There are two main groups of constituents: the terpenes (monoterperpenes, sesquiterpenes) and

the oxygenated compounds (mainly esters, aldehydes, ketones, alcohols, phenols, and oxides) [2, 22].

Bergamot oil contains 5-methoxypsoralen, which can cause phototoxic reaction (berloque dermatitis). Coconut oil, corn oil, linseed oil, olive oil, peanut oil, sesame oil, and safflower oil can develop acne/folliculitis [2]). Irritant dermatitis due to *Nigella sativa* black cumin oil has been reported as well as immediate contact reactions to caraway seed oil, cassia oil, clove oil, and peppermint oil [23].

Allergic contact dermatitis has been related to more than 80 essential oils including lavender oil, geranium oil, ylang-ylang oil, tea tree oil, and lemongrass oil. Patients have been sensitized to essential oils from perfumes, aromatherapy, homeopathic preparations, toothpastes, mouthwashes, foods, and drinks.

Most of the cases of allergic contact dermatitis are occupational, affecting especially aromatherapists, masseuses, bar workers, citrus fruit pickers, hairdressers, beauticians, bakers, cooks, confectioners, grocers, and housewives [23].

In general the dermatitis starts on the hands and may progress to other skin areas such as the forearms, neck, and face, but also to legs or other disseminated areas. Systemic exposure in sensitized individuals has resulted in anaphylactic reactions and systemic contact dermatitis. In addition, the volatile nature of these oils may cause airborne allergic contact dermatitis [23].

Frequently, allergic patients can react to various oils because of common ingredients or multiple sensitizations. Often there is co-reactivity to *M. pereirae* and/or colophonium. Some oils are allergenic only after photo-oxidation due to light, oxygen, warmth, and moisture, which may create degradation products that are moderate or strong sensitizers [23].

The screening allergens for fragrance allergy in patch testing are fragrance mixtures I and II (Tables 29.6 and 29.7). Most of their chemicals are constituents of essential oils. In fragrance mixture I, cinnamic alcohol is found in hyacinth oil, cinnamic aldehyde (cinnamal) in cinnamon and patchouli oils, eugenol in patchouli and clove oils, and isoeugenol in ylang-ylang oil. Geraniol

Table 29.6 Fragrance mix I [1]

Substance	Concentration
Amyl cinnamal (α-amyl cinnamal)	1%
Cinnamyl alcohol (cinnamic alcohol)	1%
Cinnamal (cinnamic aldehyde)	1%
Eugenol	1%
Geraniol	1%
Hydroxycitronella	1%
Isoeugenol	1%
Oak moss absolute (*Evernia prunastri*)	1%
Sorbitan sesquioleate	5%

Table 29.7 Fragrance mix II [1]

Substance	Concentration
Citronellol	0.5%
Citral	1%
Coumarin	2.5%
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral)	2.5%
Farnesol	2.5%
α-Hexyl cinnamal	5%

is the main component of rose and palmarosa oils and is present in most essential oils such as geranium, citronella, lavender, and jasmine oils. In fragrance mix II, citral is the main component of lemongrass oil, farnesol is a sesquiterpene alcohol present in many essential oils, citronellol in Bulgarian rose oil, hexyl cinnamic aldehyde in chamomile oil and coumarin in the essential oils of a large number of plants.

The diagnosis is confirmed by patch testing performed with standard trays that contain fragrance mixes I and II, *Myroxylon pereirae* (balsam of Peru), perfume series, essential oils commercially available for patch testing, and the patient's own products [22].

Pseudophytodermatitis

Although this eruption appears to be due to plants, it may derive from other sources concomitant with them. It can be produced by arthropods or fungi that infest wheat, barley, rye, beans, sugar, and dried fruits. The contact with poison hairs of caterpillars may also provoke urticaria, papular eruption, and even vesiculation and

Fig. 29.18 Family Megalopygidae

necrosis. This is common in Brazil because of the Megalopygidae family [24]. Certified azo dyes applied to the skin of oranges and grapefruits rarely lead to dermatitis. The reactions resulting from contact with plant insecticides (chloronaphthalenes) used for protection may cause dermatitis, initially diagnosed as plant dermatitis. In folk medicine, those who use baths with a mixture of plants and antiseptics can develop dermatitis as well. Sometimes the culprits of these reactions are the antiseptics and not the plants, as thought initially [1, 7] (Fig. 29.18).

Complementary Examinations

Samples of all of these plants must be obtained. These samples will be sent to a botanist to identify them. Armed with the names of the plants, one can turn to the literature. If it is an allergenic plant, a patch test can be performed.

If contact urticaria is suspected, a prick test through the crude material or by the prick by prick method can be performed. Plant materials can be crushed and diluted with saline to be pricked [3].

Irritant plants often cause confusing patch-test results and should be avoided. Chemical burns leaving scars may occur, so identifying them is essential. If an additional sensitization is sus-

pected, it is advisable to use serial dilutions of an extract to confirm the irritant threshold in control subjects [2].

Patch testing with standard trays can be useful, but sometimes provide indirect information. For example, balsam of Peru is important to identify allergy caused by some plants such as conifers, cinnamon, citrus peel, vanilla, and ginger; fragrance mix for cinnamon, cloves, jasmine, *Eucalyptus*, *Citronella*, *Pelargonium*, colophony, and turpentine to conifers and *Eucalyptus* [2].

It is possible to carry out tests with extant plant material. Several parts of the plants such as roots, leaves, flowers, and fruits may be used. Leaves and petals should be lightly crushed, and stalks and thick leaves should be cut into thin slices. It is important to use the piece of the plant suspected to cause the reaction. Different specimens of the same species may vary in the concentration of allergens and the concentrations can modify in an individual plant depending on the season, degree of watering, and its general health. A mature specimen is usually more allergenic than an immature one, although the reverse may occur [1, 2]. Extracts of plant material may be used for testing in order to isolate chemically elicited responses from those caused by physical features of the plant such as spines, hairs, and raphides [2].

Wood should not be tested as is, because of the risk of irritation and active sensitization.

Wood dust can be tested when diluted 10–20% in white petrolatum.

Apparent cross-reactions between botanically unrelated plants that contain similar or identical allergenic substances may occur. True cross-sensitization is also described [2].

Photopatch testing is rarely of value in plant allergy investigation, since well-documented photocontact allergy is only described for *Parthenium hysterophorus* in India. However, repeated exposure to volatile plant allergens, notably sesquiterpene lactones, sometimes leads to a syndrome of persistent light reactivity or even a chronic actinic dermatitis [2].

Tissue histology may be helpful not only for differential diagnosis involving other conditions but also in distinguishing allergic contact dermatitis from irritant contact dermatitis, although a histologic overlap in features can be observed. In contrast to allergic contact dermatitis, the exocytosis and spongiosis seen in irritant contact dermatitis is accompanied by prominent epidermal hyperproliferation. In general, structural changes in the stratum corneum, karyorrhexis, pyknosis, and the presence of superficial vesicles with neutrophilic infiltrate are all more characteristic of an irritant contact dermatitis than an allergic contact dermatitis reaction. Sometimes the presence of trichome remnants is seen under polarized light from a biopsy specimen [5].

Diagnosis

Since the history is very important for the diagnosis of phytodermatitis, it is essential to ask the patients about their occupation, hobbies, and recent excursions during which they may have had contact with plants. Regarding occupational exposure, it is necessary to know how the patient works with plants, which parts of the plant come into contact with the skin, and the extent to which such contact occurs. Other important information includes the onset of the first symptoms, the initial site of onset, sites of subsequent spread, improvement or worsening when the patient returns to work, and whether others have experienced similar symptoms in the workplace.

Moreover, the clinical appearance, even if acute or chronic, helps to diagnose the condition.

If phytodermatitis is suspected, complementary examinations may be done according to the suspected plant dermatitis reactions already described.

> **Box 29.2 Diagnosis of Dermatosis by Plants**
> History of exposure
> Occupation, hobbies, and recent excursions
> Onset of the first symptoms, the initial site of onset, sites of subsequent spread, improvement or worsening periods
> Dermatitis or contact urticaria
> Topography of lesions
> Prick test for contact urticaria
> Patch tests for allergic contact dermatitis

Differential Diagnosis

Urticaria and angioedema due to other causes including drugs may be differentiated from contact urticaria due to plants. The latter lasts at least 1 day and is limited to the contact area, while the former can spread and have a longer duration.

Drug eruptions such as erythema multiforme, pemphigoid and other autoimmune bullous conditions, herpes, and dyshidrotic eczema may be excluded if acute contact dermatitis reactions, either allergic or irritant, are suspected. Idiopathic photodermatosis such as polymorphic light eruption or diseases with chronic photosensitivity such as atopic dermatitis and lupus erythematous, pellagra, and porphyria are differential diagnoses if airborne contact dermatitis or photoallergic contact dermatitis is suspected. Chronic reactions caused by irritant or allergic contact dermatitis may be differentiated from other chronic eczemas such as atopic, discoid, stasis, asteatotic, circumscribed neurodermatitis, eczematous drug eruptions, and infective dermatitis. Furthermore, chronic eruption due to glochids (irritant dermatitis) may cause a severe pruritus simulating scabies or prurigo.

Bullous fixed drug eruption with hyperpigmentation, and drug-induced hyperpigmentation

reactions such as flagellate pigmentation caused by bleomycin, resemble phytophotodermatitis.

Therapeutic Approach

After the identification of the plant responsible for contact dermatitis, avoiding its contact is the next step. Wearing gloves and barrier creams may be helpful, but sometimes the patients may consider changing the workplace or even their occupation. Tulipalin A (α-methylene-γ-butyrolactone) present in *Alstroemeria* and Liliaceae penetrates through vinyl gloves, so nitriles are indicated for protection. It was recently shown that vinyl, polyethylene, and latex gloves are likely permeable to plant allergens such as α-methylene-γ-butyrolactone, primin, and diallyl disulfide. The catechols in urushiol are soluble in rubber, so vinyl gloves may be used for protection against Anacardiaceae plants. Quaternium 18-bentonite and ricinoleic acid (mamona oil) are indicated for use as a barrier cream to reduce the percutaneous penetration of the urushiol, cardol, and other cross-reacting agents [1, 7, 16].

Acute dermatitis must be treated quickly, using potent corticosteroid creams such as betamethasone (0.05–0.1%) or clobetasol (0.05%), once or twice a day associated with wet dressings and cold applications until its regression. In severe cases systemic corticosteroids are used with a moderate to high daily dose for a short period (0.5–1 mg/kg/day for 3–7 days). If the dermatitis was caused specifically by calcium oxalate raphides, the symptoms may improve simply by aggressively irrigating the affected area to remove the crystals. Glochids, trichomes, and spines will often continue to cause irritation as long as they are embedded in the skin. Therefore, their removal from skin with forceps followed by the use of glue and gauze is important (the gauze is pulled off the skin after the glue dries). Low-molecular-weight heparin was tried in three cases of severe reaction of phytophototoxic dermatitis due to *Chenopodium album* and *Plantago lanceolata*, and was

reported to have prevented the development of necrosis. Severe forms of phytophotodermatitis caused by fig in sun-tan lotions may be used in burn treatment units. On the other hand, the chronic forms may require corticosteroid ointments with emollients or steroid-sparing agents such as tacrolimus 0.1% until healing. Photochemotherapy or even immunosuppressive treatments such as azathioprine or cyclosporine can be tried for severe and intractable phytophotodermatitis with or without persistent light reactions [3, 5, 9].

Hyposensitization has been attempted, with limited success. There is no scientific basis behind this practice and the risk of toxic side effects should be considered [3].

Conclusion

Although plants can cause all of the reactions reported herein, the frequency of these events is relatively low. Irritant reactions are commoner but often trivial, and the other reactions may be avoided by protection measures. On the other hand, we depend on the plant kingdom not only as a source of food but also for medicines. In addition, they are used in fragrant and emollient oils by aromatherapists. Evening primrose oil, rich in unsaturated fatty acids, is used for atopic eczema treatment. Synthetic pyrethroids are used in natural insecticide while pyrethrum is useful for the treatment of scabies and lice. Tea tree oil has antimicrobial effects. The irritant chemical constituents of several plants are used therapeutically: podophyllotoxin is used in the treatment of genital warts, ingenol mebutate in actinic keratosis and skin cancers, and etoposide in leukemias with cutaneous involvement and histiocytosis X. Colchicine is an alkaloid used topically or systemically. Herbal medicine employs a mixture of plants to obtain a synergistic effect greater than its constituents. It is used in Chinese medicine especially for the treatment of atopic children. Given the multiple medicines synthesized from the plants, it is of great importance to preserve them [2].

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Suggested Literature

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Skin Lesions Caused by Venomous Animals

30

Vidal Haddad Jr.

Key Points Summary

- Injuries and envenomations caused by animals are common in workers in certain professional activities, such as farmers, workers in forest areas, and fishermen
- There are first-aids measure that should be known by the Health Teams when an envenomation occurs, and preventive measures may be disclosed to these workers through targeted campaigns.
- The repercussions on the skin of the victim demonstrate the importance of the dermatologist's role in solving the problem.

Introduction

Many terrestrial and aquatic animals utilize toxic substances they store or produce in order to defend or attack other animals. The envenomations cause frequent cutaneous manifestations, ranging from simple macules without any repercussions for the victim to severe tissue necrosis and even death [1, 2].

This chapter is divided into two parts: (1). Envenomations Caused by Animals (Injuries by Venomous/Poisonous Animals) and (2) Injuries Caused by Aquatic Animals.

Envenomations Caused by Animals (Injuries by Venomous/Poisonous Animals)

Clinical, Diagnostic, and Therapeutic Aspects of Envenomations with Cutaneous Impact

Invertebrates

The spiders that have major repercussions for Dermatology are the brown spiders of the *Loxosceles* genus, which live in dark and dusty places such as garages, warehouses, sawmills, and workshops. These spiders cause occupational injuries with some frequency [1–3]. The venom may cause extensive skin necrosis and in about 5% of cases causes hemolysis that can provoke acute kidney failure [1–3].

Brown spiders are reclusive spiders that exist virtually across the globe. They only bite when pressed against the body of the victim. Manifestations begin with a burning sensation or even no pain whatsoever. After about 6 h an ischemic area is delimited: a plaque with cyanotic,

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Fig. 30.1 *Loxosceles* spider and marble plaque 6 h after the bite. Loxoscelic ulcer (2 months of evolution) (Photos: Vidal Haddad Jr)

pale, erythematous colors is observed, featuring marble plaque (Fig. 30.1). At this time it is possible to observe hemorrhagic blisters on the plaque, which are very painful. The plaque gives rise to full necrosis in about 1 week, and a tightly adherent eschar remains for up to 3 weeks, slowly detaching. At this stage the eschar is painless. When the eschar finally detaches it shows a deep ulcer of large diameter, with a granular base and high edges. Confusion with specific ulcers is common, especially with cutaneous leishmaniasis. The ulcer healing process is slow and resolves only after months [1–3].

The differential diagnosis of necrotic araneism is conducted according to the phase of the envenomation: initially cellulitis, erysipelas, and necrotizing fasciitis must be excluded. In the necrotic phase, there may be confusion with skin necrosis caused by other animals (such as snakes), drugs, and bacteria. In the ulcer stage, it is necessary to differentiate it from other ulcers of chronic disease, such as those seen in mucocutaneous leishmaniasis, paracocciodioidomycosis, sporotrichosis, cutaneous tuberculosis, and squamous cell carcinoma. The histopathologic examination allows elimination of other illnesses, since in cutaneous loxoscelism there is neovascular and fibrosis formation, but no granulomas or tumor aspects.

Treatment of cutaneous loxoscelism also is initiated according to the phase of the injury. Early diagnosis reduces the clinical manifestations and the use of antivenom is the most appropriate approach, although there is an option to employ sulfone (200 mg/day) to prevent diapedesis of neutrophils and reduce the necrosis. The use of corticosteroids is controversial. In later stages, it is possible to use skin grafts to repair ulcers [1–3].

Bees and wasps can cause serious envenomations and allergic problems. Massive attacks have occurred after the spread of bees of the *Apis* genus from Africa to America, the victims being mainly farmers and beekeepers. More than 500 stings signifies major risk of death and the venom, rich in phospholipases, causes multiple organ failure. Anaphylactic shock is possible and should be treated with injectable corticosteroids, promethazine, and millesimal adrenaline. In a multiple attack, an important step is the careful removal of the remaining stingers to enable alteration of the outcome of envenomation, since some stinger glands discharge their content after introduction into the skin [1, 2, 4, 5].

Among the ants of interest to the dermatologist are the *Solenopsis* genus, the imported fire ant or lava-pés ant, which can cause allergic

Fig. 30.2 Massive injuries caused by imported fire ants (*Solenopsis invicta*), 2 days after the stings (Photos: Vidal Haddad Jr)

manifestations of similar appearance to envenomations by bees, including anaphylaxis. The main victims are children and persons with walking difficulty [6]. At the time of sting, an erythematous papule forms (wheal). Within about 24 h, a sterile pustule arises resulting from polymorphonuclear neutrophil diapedesis (Fig. 30.2). Secondary infection is very common and can aggravate the envenomation [1, 2, 6, 7].

The differential diagnosis includes subcorneal pustulosis, pustular psoriasis, and other pustuloses, but the work-related history helps the differentiation. Treatment consists of antihistamines and topical corticosteroids, alternated with topical antibiotics.

The venomous animals that probably cause most envenomations in humans are moth larvae. Caterpillars of Megalopigidae and Saturnidae families (Fig. 30.3) cause intense pain at the site of the contact and skin lesions that can range from mild erythematous macules to superficial skin necrosis. The venom is within the bristles that cover the bodies of the animals. The pain can be controlled with segmental anesthetic infiltrations. If the pain returns after 2 or 3 h, repeating the procedure is indicated [1, 2].

Envenomations after contacts with colonies of caterpillars of the *Lonomia* genus are characterized by generalized bleeding, evidenced by cutaneous ecchymosis [1, 2, 8]. Some moths (such as the *Hylesia* genus) cause pruritic erythematous papules and late foreign body granulomas in exposed areas. The moths are attracted to lights in coastal regions or forests. The stinging hairs are dispersed in the air when the moth is struggling against the light and penetrate the human skin. Treatment consists of uses topical corticosteroids and antihistamines. The caterpillars of the moth *Premolis semirufa* ("pararama") inhabit rubber trees and cause permanent arthrosis of the fingers in sap collectors for the production of rubber. Pararamosis is considered an occupational disease [9].

Beetles of the Meloidae family (*Lytta* and *Epicauta* genera) produce cantharidin, whose irritant effects are used in dermatology: controlled and diluted amounts of the substance have a rubefacient effect. Rove beetles (Staphylinidae family, *Paederus* genus: Fig. 30.3) are producers of pederin, a crystalline amide with powerful caustic and vesicant actions, soluble in water and alcohol, able to block mitosis acting in cellular DNA. Vesicant beetles are common near artificial light sources and crops. The most frequently affected site is the cervical region, but the face, arms and legs, and any exposed area may present lesions [1, 2, 10, 11]. The envenomations can be classified as

Fig. 30.3 Caterpillar of the Megalopigidae family and envenomation on the hand of a child (the pain is not proportional to the size of the lesions). Beetle of the *Paederus* genus and vesicles and erythema on the arm of a victim. Stink bug (Pentotomidae) and erythema and lesions on the hand of a biologist (Photos: Vidal Haddad Jr)

mild, moderate, and severe. The latter manifests systemic phenomena such as nausea, vomiting, and fever [1, 2, 10, 11].

After the contact the skin becomes erythematous, which is accompanied by itching, burning, and vesicles that evolve to the formation of sterile pustules, exulcerations, and crusts [10, 11]. The lesions resolve in about a week, leaving erythematous macules or temporary residual hyperchromia. The lesions are elongated or linear, reproducing the act of rubbing the insect against the skin, and should be differentiated from contact dermatitis (from perfumes, for example), phytophotodermatitis, herpes zoster, herpes simplex, pemphigus, and envenomation by caterpillars [1, 2]. Initial treatment is through intensive washing with soap and water. Late lesions must be treated with potassium permanganate compresses twice daily and corticosteroid creams.

If there is secondary infection, the use of systemic antibiotics is necessary.

Some insects of the Pentatomidae family (stink bugs) were recently reported to be related to vesicular and erythematous plaques in the same regions affected by vesicant beetles, which are accompanied by burning and pruritus [12] (Fig. 30.3). Treatment is similar to what is used for beetle contacts.

Millipedes are animals with segmented lateral glands in each segment that produce cyanide or quinones to repel predators. These fluids may be ejected from distance and cause erythema and brown or black pigmentation in the affected skin. The accident occurs most often when the victim pulls on a shoe, as the animal enters human habitats and seeks dark places to take refuge. This dermatitis is observed frequently in construction workers while changing

footwear. The hyperchromic lesions may persist for months [13].

Initially, the use of alcohol and ether on the site is encouraged, since they function as solvents of venoms. Injuries in humans caused by centipedes are observed sporadically and pain is the main symptom, with mild erythema and edema occurring locally [1, 2, 13].

Snakebites

Envenomations by snakes occur more on the lower limbs and in men, reflecting the rural activity of the victims. They are mainly occupational accidents, occurring frequently in poor countries of tropical regions. In South America, the snakes that cause envenomations with dermatologic manifestations belong to *Bothrops* and *Lachesis* genera (pit vipers: Fig. 30.4), While the *Bothrops* genus is responsible for about 90% of snakebites in Brazil, bushmasters rarely have proven envenomations, being snakes of primary forests that are inaccessible to humans [1].

The venom of *Bothrops* snakes is coagulant and proteolytic, causing paradoxic bleeding depletion of clotting factors and important local necrosis. Initially, intense edema and erythema at the point of the bite is observed. The site can present hemorrhagic blisters that become necrotic, resulting in deep ulcers (Fig. 30.4). If there is bacterial infection the condition worsens, and envenomations treated at a later stage can lead to death or severe sequelae. The fatal cases, however, are associated with bleeding and infections and not with necrosis [1].

The differential diagnosis is the same as with other skin inflammations and necrosis, such as erysipelas and vasculitis (acute phase) and obliterating vascular diseases (in later stages). The history usually helps the suspicion.

Treatment of snakebites necessarily uses snake antivenom in the early stages, and cleaning measures and debridement of necrotic areas and ulcers in the late stages. Tying a tourniquet on the compromised member, which can aggravate the local necrosis [1], must be avoided.

Injuries Caused by Aquatic Animals

Injuries caused by marine animals are frequent (1 every 1000 occurrences in coastal cities) [1–5]. Most of these accidents occur as a result of human carelessness, since stingers, teeth, fins of rays or some fish, and various types of venoms are part of complex defense mechanisms of representatives of marine fauna. It is rare to observe an incident whereby the animal is not provoked or touched abruptly (e.g., when it is not stepped on or being removed from hooks) [1–5]. The first rule to avoid injuries, therefore, is to not touch any animal without good reason. The second is to respect the fact that venomous animals keep their venom active even after death, such as fish and jellyfish lying dead on beaches.

Fig. 30.4 *Bothrops jararaca* and envenomation of a farmer. Note the necrosis and the blisters with hemorrhagic content (Photos: Vidal Haddad Jr)

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Cnidarians

About 25% of marine envenomations are caused by cnidarians, especially the jellyfish and Portuguese man-of-war (Fig. 30.5), [14–18]. The clinical manifestations of envenomations by cnidarians is typical, with onset shortly after contact with the animal. Straight or rounded erythematous linear plaques and severe pain are the main aspects (Fig. 30.5). First-aid measures to injuries by cnidarians require iced seawater compresses (or application of cold packs) on the lesions (for pain control) and vinegar baths (to block the discharge of nematocysts still present in the skin). Freshwater application can aggravate the envenomation by discharging intact nematocysts adhered to the skin. Difficulty in controlling the pain, dyspnea, cough, coryza, and cardiac arrhythmia may be indicative of severity and requirement for hospitalization [14–18].

Sea Urchins

Sea urchins are responsible for almost 50% of the injuries caused by aquatic animals in Brazil (Fig. 30.6). These may occasionally be venomous, but cause more problems because of the difficulty in extracting the spines. The literature reports that about 40% of patients who do not completely remove the thorns have fever, local pain, painful nodules, and other complications. Extraction of the spines is done using thick needles [14–18].

Fish

Injuries by venomous fish make up 25% of those caused by aquatic animals, with catfish being responsible for the majority of wounds (Fig. 30.7), followed by stingrays (Fig. 30.7) and scorpionfish (Fig. 30.7). Accidents by

Fig. 30.5 Jellyfish (*Chiropsalmus quadrumanus*), Portuguese man-of-war (*Physalia physalis*), and a typical injury in a bather (Photos: Vidal Haddad Jr)

Fig. 30.6 Black sea urchin (*Echinometra lucunter*) and spines in the human skin (Photos: Vidal Haddad Jr)

freshwater catfish (mandis) and freshwater stingrays are also commonly seen in freshwater environments [14–18].

Injuries caused by fish present varying severity, depending on the fish: the pain caused by an envenomation from a stingray or scorpionfish is excruciating, while envenomations by catfish are less painful. The effects of all fish venoms are similar: pain and skin necrosis. Fish venoms are thermolabile and the application of or immersion in hot water, to tolerable extent, by 30–90 min greatly improves the pain. Additionally the vasodilatation provoked by the high temperature decreases the ischemia promoted by the venoms. The patient should be referred to hospital for wound cleaning and extraction of possible fragments of barbs or spines in the wound [14–18].

Risk factors differ in relation to accidents by aquatic animals: underwater fishermen and scuba divers are exposed to contact with sea urchins in rocky cliffs and are injured frequently. Another risk factor is determined by venomous or

Fig. 30.7 Marine catfish (*Genidens genidens*) and injury in a human. Marine stingray (*Rhinoptera* sp.), Scorpionfish (*Scorpaena plumieri*), and wounds provoked in professional fishermen (Photos: Vidal Haddad Jr)

traumatic fish during underwater activity. Thus, scorpionfish, which remain motionless on the seabed and are almost invisible, can cause accidents to divers. The imprudence of scuba divers in touching stingrays, barracudas, and sharks can also bring problems, as well as fishing for large fish such as large groupers.

Professional fishermen are injured when separating shrimp from the rest of the content of driftnets, which may include jellyfish, small moray eels, and catfish. The injuries caused by fish are the main occupational disease in freshwater and marine professional fishermen [14–18]. Finally, students researching marine biology are at risk because collecting and manipulating seemingly harmless fish can cause wounds, dermatitis, and painful conditions. Several other fish besides the aforementioned may produce poison, although accidents are rare. First-aid measures are indicated to control the symptoms of injuries from aquatic animals in most cases, but persistent pain, swelling, or erythema at the injury site may require hospitalization.

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Occupational Dermatosis

31

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Key Points Summary
- Occupational dermatoses are very common and an authentic public health problem
- Occupational dermatosis may be caused by several chemical, physical, and biological agents
- Contact dermatitis is the most common type of occupational dermatosis
- Occupational dermatosis occurs more often in housekeeping, civil construction, health sector, cosmetic sector, food and catering industries, and metal industries
- Main point of therapy is to eliminate the identified causative agent

Introduction

Occupational dermatosis (OD) can be defined as any alteration on the skin, mucosa, and/or adnexa, directly or indirectly caused, maintained, or aggravated by anything used during professional activity or present in the work environment [1].

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Epidemiology

OD ranks second among the most frequent occupational diseases, after repetitive stress injury. Contact dermatitis (CD) is the most common type of OD, accounting for 80% of ODs. The annual incidence rate of CD is 0.5–1.9% [2]. The incidence is growing because of contact with new products [3, 5].

In many countries the prevalence of ODs is difficult to assess because the studies are based on analyses of contact allergy tests. It is not mandatory for workers to give a notification of OD diagnosis, and many choose not to, fearing for their job stability. Occupational skin cancer is underestimated because it is difficult to establish a causal link owing to the long latency period. Infections are also challenging to evaluate because they may be acquired outside the occupational activity. The etiologic diagnosis of CD depends on occupational history, physical examination, and contact allergy testing.

Irritant CD (ICD) is more common than allergic CD (ACD) (4:1). Psoriasis, atopic dermatitis, and ICD predispose to ACD [6–9].

The hands are usually the areas most affected by CD because of the handling of multiple substances, excess humidity, and/or friction. It is important to note that education and protection measures decrease the prevalence of CD [10].

Young individuals are more affected by OD, owing to professional inexperience and lack of a

thickened stratum corneum. For males, the most frequent sensitizers are cement and rubber, and for females nickel, which is usually a non-occupational contact, related to wearing jewelry [6, 7, 11]. The lesions appear primarily on the hands and eyelids, caused by allergen transportation.

Individuals from African and Asiatic ethnicities are more protected from the degenerative and neoplastic actions of sunlight, but African individuals develop keloids more frequently than Caucasians.

Causative substances vary according to occupation. Fragrances are common sensitizers in the general population, including among health and beauty professionals [12].

Etiopathogenesis

ODs may be caused by several chemical, physical (light, radiation, trauma, pressure, heat, cold), and biological (viruses, bacteria, fungi, parasites, plants, animals) agents. These agents affect the skin through contact (contactants: localized dermatitis) or via the bloodstream (endogenous agents: disseminated dermatitis) and can be introduced by percutaneous absorption, inhalation, ingestion, inoculation, and/or injection.

Psychic alterations may lead to linear or geometric lesions (factitious or self-inflicted dermatitis), which can also be caused purposefully to obtain medical leave or indemnification. Inappropriate treatment may mask the initial clinical picture and cause iatrogenic CD.

CD is the most common type of OD. In CD, the inflammatory process begins when the contactant crosses the skin barrier. Keratinocytes induce the production of cytokines, which stimulate other keratinocytes and other cells, such as Langerhans cells.

ICD: tumor necrosis factor α (TNF-α), interleukin (IL)-2, and IL-6 levels are increased. The cytokines TNF-α, interferon (IFN)-γ, and IL-1 stimulate production of intercellular adhesion molecule 1 (ICAM-1), which promotes non-specific antigen adhesion in leukocytes and other cells.

ACD: cell-mediated immune response predominates in inflammatory reaction.

It occurs in three phases:

- Induction or immunization: afferent pathway, lasts 5–10 days. Hapten, a low molecular weight substance, penetrates the stratum corneum and binds to a protein, forming an antigen conjugate, which binds to glycoprotein from plasma membrane of skin Langerhans and dendritic cells. These cells present the antigen to CD8+ T cells in the regional lymph node, and are regulated by inflammatory cytokines and adhesion molecules. In the presence of IL-12, the T-helper 0 (Th0) cells in lymph nodes differentiate into Th1 and Th17 cells via downregulation, and circulate in the blood, disseminating sensitization. In general, sensitization is progressive and permanent.

- Elicitation: during a new contact with the same allergen, with loss of cell-mediated immune regulation by regulatory T cells, which is associated with cell tolerance, there is activation of cell response mediated by cytotoxic T lymphocytes, associated with keratinocyte activation. The production of inflammatory cytokines and adhesion molecules will lead to the clinical picture of CD [5].

- Resolution: end of the inflammatory reaction that starts approximately 48 h after antigen stimulation. The immune reaction is inhibited by IL-10, IFN, transforming growth factor β, mast cells, basophils, and CD8+ suppressor T lymphocytes [6, 7].

Phototoxic dermatitis is based on a nonimmunologic mechanism. It increases the reactivity of the skin to ultraviolet rays and/or visible radiation. It is a sunburn whose energy is absorbed by a photosensitizer. The commonest phototoxic agents are: tars such as creosote for wood preservation, plants containing furocoumarins (psoralens) such as citrus fruits (lemon, bergamot orange) sulfonamides, chlorpromazine, griseofulvin, tetracyclines, nonsteroidal anti-inflammatories, and cadmium sulfide [13].

Photoallergic dermatitis is based on an immunologic mechanism. The reaction to a photoallergen is based on the same immunologic mechanism as simple contact dermatitis.

Photocontact allergens: phenothiazines, sulfonamides, topical nonsteroidal anti-inflammatories, sun creams such as para-aminobenzoic acid, hexachlorophene, perfumes, halogenated salicylanilides [13].

Clinical Presentation

> **Box 31.1 Clinical Presentation of Occupational Dermatoses**
> The most common ODs are acne, cancer, keratosis, contact dermatitis, dyschromias, erythema, papular eruptions, foreign body granuloma, infections, onychias, purpuras, and ulcerations.

Contact Dermatitis

CDs account for 80% of ODs; they are usually eczematous and are classified as ICD and ACD (Box 31.2) [3–5].

ICD is usually caused by caustic agents, and can be absolute or relative, depending on the irritant and its concentration, pH, and exposure period. Irritants in contact areas lead to the quick (absolute) or gradual (relative) appearance of lesions, after several successive exposures. This type of CD does not require previous sensitization and, in general, a cure is possible after stopping contact with the causative substance. The relative ICD presents erythema, desquamation, keratosis, and fissures. In the hands it is more intense in the dominant hand and more frequent in the palm region. The absolute ICD resembles burns, with blisters and/or necrosis, ulcerations, and crusts (Figs. 31.1 and 31.2).

In ACD, lesions appear in the areas that had contact with the sensitizer, where they are

Fig. 31.1 Chemical burn by absolute irritant contact dermatitis (hypochlorite)

more intense, but also in regions far from where contact happened. Severity and extension of lesions may worsen each time the individual is exposed to the allergen, and manifestations may appear more quickly. They may occur months or years after contact with the allergen, but it takes at least 1 week to present manifestations. The eczematous lesions may be acute (erythema, edema, vesicles, and discharge), subacute (predominance of discharge and crust formation), and chronic (desquamation, lichenification, keratosis, and fissures) (Figs. 31.3, 31.4, and 31.5).

Noneczematous CDs are rarer, and include lichenoid contact dermatitis, contact urticaria, contact acneiform eruptions, photodermatosis, contact leukoderma, contact purpuric eruption, erythema multiform-like contact, contact pustular eruption, keratotic contact dermatitis, and hyperchromic contact dermatitis. Phototoxic dermatitis is a sunburn. Photoallergic dermatitis appears as eczematous lesions in the areas that had contact with the allergen, but also in sun-exposed regions (Figs. 31.6 and 31.7)

Fig. 31.2 Relative irritant contact dermatitis (soaps, detergents, wet work in houseworker)

Fig. 31.3 Allergic contact dermatitis (metal of musical instrument) in a musician

Fig. 31.4 Allergic contact dermatitis by rubber additives of gloves

Fig. 31.5 Allergic contact dermatitis by rubber additives of boot

Fig. 31.6 Phototoxic contact dermatitis (lemon)

Fig. 31.7 Phototoxic dermatitis by wood (*Andira vermis*)

Other Occupational Dermatoses

Acne: caused by pure saturated oils, with follicular obliteration especially on the forearms and thighs (Figs. 31.8 and 31.9)

Chloracne: caused by chlorinated hydrocarbons, which cause acneiform lesions with many cysts. It may cause severe systemic alterations (Fig. 31.10).

Cancer: basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma. The main oncogenic agent is ultraviolet radiation. Other risk agents are ionizing radiation and chemical substances, such as arsenic, chromium, and benzo[a]pyrene. It is difficult to establish the occupational link because of the latency period (Figs. 31.11 and 31.12).

Keratoses (diffuse and calluses): generally of traumatic origin, they can also be premalignant lesions, such as arsenical keratosis, solar keratosis, and leukoplakia (Fig. 31.13).

Dyschromias:

- Melanodermas: postinflammatory hyperpigmentation by melanin and by burns. Riehl's melanosis occurs on the face of metal workers, probably due to ACD to cutting-fluid preservatives. Phytophotodermatitis hyperpigmentation is another example.

Fig. 31.10 Chloracne (polyhalogenated aromatic hydrocarbons of pesticides)
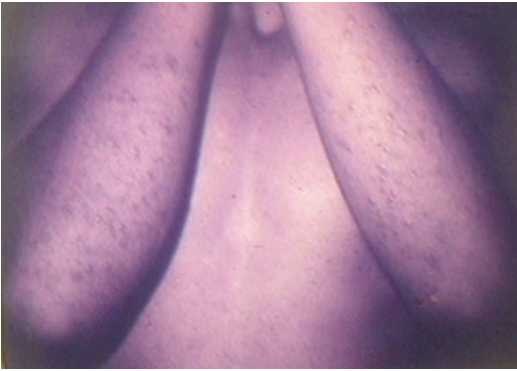
Fig. 31.8 Oil acne

Fig. 31.9 Oil acne

Fig. 31.11 Arsenical basal cell carcinoma in the arm

Fig. 31.12 Squamous cell carcinoma in agricultural worker caused by ultraviolet rays

Fig. 31.13 Traumatic keratosis (press clothes worker)

- Other pigments: lead, mercury, arsenic.
- Leukoderma: chemical vitiligo caused by hypopigmentation substances, such as rubber hydroquinone (Fig. 31.14).

Erythema:

- Perniosis: caused by cold, in cold storage workers (Fig. 31.15).
- Erythema ab igne from localized contact with heat.

Papular eruptions:

- Urticaria caused by latex individual protective equipment (IPE).
- Polymorphous light eruption in outdoor workers.

Foreign body granuloma: Very common, caused by numerous materials, such as thorns, wood, or iron splinters, e.g., "hair pilonidal sinus disease of barbers and animal groomers" (Fig. 31.16).

Fig. 31.14 Chemical vitiligo by hydroquinone as rubber additive

Fig. 31.15 Perniosis (cold storage worker)

Fig. 31.16 "Hair pilonidal sinus disease of barbers and animal groomers"

Fig 31.17 Mycobacteria infection by *Mycobacterium marinum*

- Mycoses: paracoccidioidomycosis, chromomycosis, sporotrichosis, dermatophytosis, candidiasis, among others.
- Bacterial: leprosy, erysipeloid, carbuncle, atypical mycobacteriosis ("swimming pool granuloma") caused by *Mycobacterium marinum* (Figs. 31.17 and 31.18).
- Viral: milker's nodule, herpes simplex, viral warts.
- Parasitic: pediculosis capitis, scabies, American mucocutaneous leishmaniasis.

Onychias: Nails are subject to several risks.

- Traumatic.
- Infectious.

Infections: It is difficult to prove a causal relation with infections, as they may be acquired outside of work.

Fig. 31.18 Sporotrichosis in a gardener

Fig. 31.19 Leukonychia (polycythemia of methemoglobin)

- Nail dyschromias: traumatic melanonychia, leukonychia and polycythemia caused by nitrite-induced methemoglobinemia in textile industry; subungual hemorrhage (Fig. 31.19).

Purpura: coagulopathies, such as benzene-induced bone marrow aplasia, allergic vasculitis, traumatic purpura (Fig. 31.20).

Ulcerations: the specific ulcerations occur in occupational cancer and infections; the non-specific are related to trauma or burns (Fig. 31.21)

Box 31.2 Classification of Contact Dermatitis
- Irritant contact dermatitis (nonimmunologic)
- Allergic contact dermatitis (cell-mediated immunity – delayed)
- Phototoxic contact dermatitis (nonimmunologic)
- Photoallergic contact dermatitis (cell-mediated immunity – delayed)
- Allergic contact urticaria (mediated by immunoglobulin E (IgE) – immediate)
- Nonimmunologic contact urticaria

Fig. 31.20 Traumatic purpura in heel (sportsman)

Diagnosis

Box 31.3 Diagnosis of Occupational Dermatoses

Clinical: detailed history – the clinical picture should be compatible with the type of OD.

Complementary examinations:

- Patch test is the most common
- Prick test (carefully)
- RAST (radioallergosorbent test)
- Histopathologic examination
- Direct mycologic and culture mycologic

Clinical

A detailed history is crucial. The clinical picture should be compatible with the type of OD: site of the lesion, exposure to irritants and/or allergens, chronology of dermatosis, behavior of the skin condition regarding sick leave, nonoccupational exposure to the agent [8].

Fig. 31.21 Ulcerations by electric burns

Complementary Examinations

Patch test (PT): the most widely used test for OD. It allows differentiation of ICD from ACD: ICD has negative PT, and ACD has positive PT. They are performed to confirm the clinical diagnosis and for forensic purposes [6, 8]. Technical procedure: Application of patch (allergen in petrolatum or liquid test) on the upper back. Marker for the test area. Readings: two readings, the first after removal of the patch (usually day 2) and the second 2–5 days later (Figs. 31.22 and 31.23).

Prick test: for contact urticaria (carefully).

RAST: radioallergosorbent test for contact urticaria.

The *histopathologic examination* of CD skin lesion is not specific and does not differentiate CD from other types of eczemas. It is useful to clarify differential diagnoses. *Direct mycologic examination* and *culture mycologic examination* are necessary for the diagnosis of superficial or deep mycoses.

Fig. 31.22 Positive patch test (balsam of Peru)

Sectors Where Occupational Dermatosis Occurs More Often

Housekeeping

Workers who use cleaning products (soaps, detergents) comprise the occupational group more likely to develop CD [6]; however, the frequency of this OD is relatively low because of the small number of exposed individuals [7].

It may begin as ICD, which facilitates allergen penetration. The most common site is the hands, especially in individuals who do not wear IPE. The IPE can cause ICD because of sweat, powder, pH, or IPE material. Soaps and detergents, from the alkalis manipulated by these

Fig 31.23 Positive patch test

professionals, affect the skin through several mechanisms and trigger ICD. The cleaning product sensitizers are additives, preservatives, colorants, whiteners, and fragrances. Enzyme detergents rarely cause ICD or ACD [7].

Other allergens are rubber IPE that cause latex-induced contact urticaria, while rubber vulcanizers cause ACD.

Civil Construction

This industry encompasses 200 occupations: bricklayer, electrician, carpenter, tile setter, plumber, locksmith, painter, and so forth. The main risks are cement, wood, and rubber. Cement is a very fine powder. When mixed with water it acquires a pasty consistency and later becomes solid (setting). There are two types of cement: natural and artificial. The artificial type is obtained by clinker grinding (limestone + clay + gypsum) heated at high temperatures. It is classified as Portland and aluminous, the latter with 50% aluminum [8]. Portland cement receives several additives that provide different properties. In its basic composition as an ore it contains calcium silicate and aluminate, iron and magnesium oxides, alkalis and sulfates. Grout is the mixture of cement with sand, and by adding crushed stone it becomes concrete. Cement powder is very irritating (hygroscopic, abrasive, and alkaline) and, when wet, becomes more alkaline (pH > 12) and more irritating, and can cause relative ICD. When in contact with the skin for long periods of time, under pressure, friction, and occlusion, it triggers absolute ICD ("burns" and "ulcerations" from cement; Fig. 31.24). The basic cement composition is not sensitizing; however, it is contaminated by highly allergenic metals (cobalt and chromium VI, and, more rarely, nickel) from ore and its preparation technique. It can trigger acute or generally chronic ACD (Fig. 31.25). Cement additives may be irritating and sensitizing [14]. In construction works, wood is used for poles, scaffolds, doors, windows, and floors. Tropical or exotic woods and pine are the main risks for skin [14] and can cause ICD, ACD, photoallergy, and phototoxic-

Fig. 31.24 Irritant contact dermatitis of wet cement (chemical burn)

ity. Wood preservatives may cause ototoxicity (creosote); chloracne and systemic poisoning (pentachlorophenol); and ACD and systemic poisoning (mercury-based). Other risks are IPE that cause ICD and ACD because of rubber vulcanizers in 50% of bricklayers, dry skin, or ICD. They may also lead to contact urticaria and natural rubber latex anaphylaxis. Paints and adhesives (formaldehyde, epoxy, or acrylic resins), turpentine (paint solvents), and paint preservatives cause ACD. Machinery oils, fiberglass (thermal insulation), solvents, and other cleaning products cause ICD [15].

Health Sector

This sector encompasses a great diversity of professions: physicians, dentists, nurses, nutritionists, beauticians, veterinarians, and others [15]. In some countries they represent the largest occupational groups. ODs are very common in the health sector. The most studied ODs are related to medicine and dentistry. The types of dermatoses and their incidence significantly vary according to the profession and diverse medical and dental specialties. The risks for radiologists, clinicians, surgeons, and laboratory professionals are very different [16, 17]. Hands are the most affected area [13, 15]. Dermatosis can have chemical, infectious, or physical origin. The group most susceptible to these dermatoses is nurses, followed by dentists and surgeons [16].

Fig. 31.25 Allergic contact dermatitis by chromium of cement

Humidity related to the occupation and some skin conditions (atopic dermatitis, psoriasis) predispose these workers because of their use of antimicrobials and frequent hand-washing. CD in these professionals is associated with work materials (gloves, metals, epoxy and acrylic resins) and chemical substances, such as disinfecting agents and medications. ICD is the main OD. The usual agents include humidity, antibacterial soaps, gloves, antiseptic solutions, formaldehyde, laboratory materials, solvents, and polishing powders. ACD may be triggered by rubber vulcanizers, glutaraldehyde (antiseptic and X-ray solutions, used by dentists), antimicrobials (formaldehyde, povidone), resins (acrylic and epoxy for prostheses and orthopedic cements), rubber gloves, medications (penicillin, sulfa, acetaminophen, mercurial agents, phenothiazine, anesthetics such as procaine), and radiology developers. Medications are no longer the main cause, with rubber gloves additives taking over the first position. Acrylates cause pulpitis (fingertip dermatitis) in dentists. The incidence of latex contact urticaria (IgE-mediated) [5] has increased in dentists, nurses, and surgeons (5–10% of physicians are allergic to latex) since the epidemics of hepatitis and AIDS in the 1980s. Powder in gloves retains latex and as an airborne contaminant may cause allergy, urticaria, respiratory allergy, or anaphylaxis. Other causes of contact urticaria are medications, such as topical antibiotics (neomycin, bacitracin, penicillin), salicylate, chlorpromazine, and nitrogen mustard. Other common dermatoses are infections (bacterial, fungal, viral, parasitic), although it is difficult to establish an occupational link (Fig. 31.26). Even more rarely, there is chemical vitiligo from hydroquinone in radiology technicians; acneiform eruption from halogenated anesthetics; and cancer caused by formaldehyde. Less common are ODs caused by physical agents, such as trauma, and chronic friction, such as keratosis, leading to psoriasis; radiodermatitis and SCC in radiology professionals; burns (ultraviolet and infrared rays); and Raynaud's phenomenon in professionals who perform cryotherapy [16].

Fig. 31.26 Onychomycosis (*Candida albicans*)

Beautification Sector

This sector encompasses various professional activities and is one of the fastest-growing sectors in the last decade (in Brazil, it is the second largest corporate sector based on number of employees). Beauty parlors predominate and house more individuals (hairdresser, barber, manicurist, make-up artist), followed by piercing professionals, tattoo artists, and beauticians [16, 18]. At beauty parlors, several jobs are performed and the workers are in constant contact with several products. Atopy and psoriasis are predisposing factors.

Other important concepts:

- Irritants: shampoos, hydrogen peroxide, ammonium persulfate, humid work, hot air (hairdryers), gloves.
- Allergens: p-phenylenediamine is the main allergen with regard to number of cases [14] (hair dye, henna tattoos);
    - Metals (nickel and cobalt) – instruments;
    - Glyceryl-thioglycolate ("acid perms") – hair curling and straightening; ammonium persulfate – hair discoloration;
    - Latex and rubber vulcanizers from rubber gloves [8];
    - Fragrances; creams with preservatives;
    - Nail polish;

- Acrylic nails;
- Cosmetics (Fig. 31.27).
- ICD is the most common OD, and approximately 50% of experienced hairdressers present ACD [15]. ICD affects mostly assistants and trainees, owing to the humid work (hair washing).
- Contact urticaria and IgE-mediated anaphylaxis: rubber glove latex and ammonium persulfate.
- "Pilonidal sinus disease of barbers and hairdressers": foreign body granulomas from hair and beard fragments. It usually affects the bottom-most of interdigital spaces of the hands.

Food and Catering Industries

This sector includes professionals that handle foods. The largest number of OD cases is found in bakers, confectioners, cooks, homemakers, servers, and kitchen and domestic services employees. The more common ODs are ICD, ACD, dyshidrosis, burns, miliaria, phytophotodermatitis, candidiasis, bacterial paronychia, and contact urticaria due to foods and animal fluids [2]. They stay in the hands as a result of handling of multiple substances (several types of flour, onion, garlic), friction, and humid work. They usually affect the first three fingers of the secondary hand (Fig. 31.28). ICD is caused by agents included in bakery or confectionery products: sweeteners, emulsifiers, foaming components, yeast, enzymes, colorants, and aromatizers. Dermatitis from ground foods is follicular and appears on the back of the hands of bakers in contact with flour. Dyshidrosis might appear because of flour inhalation. CD in bakers presents as eczematous lesions or urticaria caused by flour, sorbic acid, and enzymes [7]. ICD is caused by pasty foods, juices, wheat, and pineapple. ACD has the following allergens: food aromatizers, spices, and food additives. [1] Fissured lesions in finger pulps are caused by garlic, onions, tomatoes, and carrots. Phytophotodermatitis is caused by celery,

Fig. 31.27 Allergic contact dermatitis in hairdresser (fragrance)

Fig. 31.28 Onychomycosis by *Candida albicans* in a baker

white carrots, parsley, orange, and lime peels. Lettuce, endive, tomatoes, and chicory cause immediate vesicular dermatitis on the hands. Contact urticaria (immediate allergy) is caused by raw fish, shellfish, shrimp, cheese, and raw potatoes. Patch tests on skin not injured by food may be negative, and the prick test may be positive. Individuals with ACD may or may not have dermatitis when ingesting foods. Cooking or digestive juices may help the foods become hypoallergenic [8].

Metal Industry

The risks involved are oils and metals. Oils may produce oil acne and chloracne.

CD is generally an irritant. ACD is generally caused by the metals nickel and chromium. Oils and fluids are used in the metal industry for cooling and lubrication. ACD due to cutting oils is rare [7], and is generally caused by preservatives and metal corrosion inhibitory agents. With automation in the metal industry, there is less contact with fluids. Patch tests with original oils may present negative results and used oils can show positive results. Since oils are irritants, it is

Fig. 31.29 Allergic contact dermatitis (worker with galvanized chromium)

Fig. 31.30 Chromium ulceration

helpful to perform control tests. In electroplating (metallic surface coating), ICD may occur because of degreasing baths (hot caustic soda or quicklime with gasoline-type solvent or sodium hydroxide). ACD is triggered by nickel and chromium baths (Fig. 31.29). Chromium also causes skin and nasal septum ulcerations [5] (Fig. 31.30).

Differential Diagnosis

The differential diagnosis of eczematous contact dermatitis is made with several types of eczemas: atopic dermatitis, nummular eczema, dyshidrosis, stasis dermatitis, and lichen simplex chronicus. Other rarer ODs have specific differential diagnoses for each dermatosis.

Therapeutic Approach

Treatment

Eliminate the identified causative agent. Treatment must start early to decrease progres-

sion of the OD and avoid sequelae. IPE, secondary infections, self-inflicted dermatoses, or medications used by the patients may cause ICD and/or ACD.

ODs can result in disability, requiring professional readjustment.

For localized CDs, in acute forms, mild liquid compresses (boric acid, saline solution, potassium permanganate) and corticosteroid creams are used. For chronic lesions, corticosteroid ointments can be used. For difficult-to-control, chronic hand dermatitis, alitretinoin (9-*cis*-retinoic acid) can be used [19]. In the case of secondary infection, a topical and/or systemic antibiotic should be added.

For extensive lesions, it is recommended to use systemic corticosteroids, tapering the dose according to the involution. For chronic use, consider the side effects of corticosteroids.

Systemic antihistamines may be used only for relieving pruritus.

For other ODs, conventional treatment is recommended for each of them.

Prevention

Preventive measures against OD and recurrences must be taken, because it causes discomfort for the worker and can result in job-related disability,

change of job position, decreased worker productivity and company performance, and increased medical and pension costs [6].

The company must adopt collective environmental protection and educational measures for its employees.

Dangerous chemical processes must be performed in automated closed systems. For the workers' individual protection, it is necessary to avoid contact with irritant or sensitizing agents, maintain personal hygiene, immediately wash contaminated areas, and moisturize them with fragrance-free creams. Clothing and locker rooms must be kept clean. IPEs are necessary (gloves, boots, bonnets, mask, and apron). Those allergic to rubber should wear vinyl gloves, and the individuals allergic to latex can also use latex-free rubber gloves or polyurethane gloves. Those allergic to acrylates can wear nitrile gloves. For jobs in which manual dexterity is essential, and in conditions with high risk of work-related accidents, gloves are not permitted [15].

The use of emollients is recommended. Barrier creams are controversial, and may be used for prevention, but not during treatment.

Workers should be given clear orientation and receive, in writing, the chemical and brand names of products and substances with which they may come into contact [8].

Glossary

Occupational dermatosis Can be defined as any alteration on the skin, mucosa, and/or adnexa, directly or indirectly caused, maintained, or aggravated by anything that is used during professional activity or is present in the work environment.

Patch test Contact allergy test in which suspicious substances are placed on the skin, usually on the back, for 48 h and two readings are taken – at 48 and 96 h (with the latter as the definitive reading). Standardized batteries are employed, with the most allergenic substances of the studied geographic region alongside specific substances, such as cosmetics or metal and others, and, if possible, the patient's own materials.

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Dermatologic Diseases in Public Health: Vital Cycle and Dermatology

Dermatology and Pregnancy

32

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Key Points Summary
- Cutaneous manifestations during pregnancy can be divided into physiologic and pathologic
- The pregnancy-specific dermatoses are classified as pemphigoid gestationis, polymorphic eruption of pregnancy, intrahepatic cholestasis of pregnancy, and atopic eruption of pregnancy
- Pregnancy has a tendency to affect the course of the immunomediated diseases, with improvement in most of the cases and worsening in others
- A watchful diagnosis and patient follow-up are crucial for treatment aimed at the prevention of maternal and fetal complications.

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Introduction

Cutaneous manifestations during pregnancy represent changes along a transient physiologic period when extreme modifications in the woman's body affect almost all organs and systems, including the skin and its appendages, to generate another human being.

Endocrinal, immunologic, metabolic, vascular, and mechanical changes occur during pregnancy. Endocrinal alterations are characterized by large elevations of estrogen, progesterone, cortisol, β-human chorionic gonadotropin, prolactin, and a variety of hormones and mediators that alter the organic functions [1, 2]. The peak levels of these hormones vary according to the gestational period, possibly reflected in cutaneous manifestations [11]. These numerous changes in the mother's body may account for gestational pathologic and physiologic cutaneous manifestations.

The immune-endocrine interaction triggers significant changes resulting in the majority of skin modifications during pregnancy [1, 2]. Most immune system changes come about in order to maintain the mother's immune system tolerance to the paternal major histocompatibility antigens expressed by the fetus [2]. Sexual steroids in pregnancy have an inhibitory effect on the activity of B cells, and high estrogen levels play a role in decreasing the number of autoantibodies. Therefore, this period is characterized by

stimulation of the innate immune system and suppression of the adaptive immune system [2].

This chapter discusses the physiologic epidermal changes in pregnancy, and the effects that pregnancy causes on preexisting skin diseases and skin diseases related specifically to pregnancy. In addition, the epidemiology, etiopathogenesis, clinical presentation, complementary examinations, and therapeutic options for each condition are outlined.

Physiologic Changes During Pregnancy

Many changes in the proteic, lipid, and glucidic metabolism occur in order to develop the fetus along the pregnancy course: increased cardiac output, hypervolemia, hemodilution, and changes in the arterial pressure; increased glomerular flow, changes in respiratory dynamics; appetitive changes, nausea and vomiting, gastroesophageal reflux, or constipation; and endocrine and immunologic changes that maintain the mother-fetus dyad and give rise to many changes, mostly in the skin [1].

Physiologic changes in the skin are the most common findings during pregnancy and deserve more attention because of the extensive cutaneous impairment, discomfort, and stigma for the patients.

Hyperpigmentation can be seen in up to 90% of pregnant women. It can occur from the 2nd month onward and increase over the gestational period [3, 4, 7]. Hyperpigmentation may be generalized (most cases) or localized; the larger the patient's phototype, the more frequent and noticeable the hyperpigmentation. Hyperpigmentation is usually light, though more intense in the usually more pigmented regions of the body, such as the abdominal median line, the nipples, the mammary areolae, the axillae, the genital area, and the upper and inner thigh areas [11] (Fig. 32.1). In black women, Futcher or Voigt pigmented lines can be seen; these lines are melanin lines along the arm's largest axis, shoulders, and posterior aspect of the legs [7]. The presentation tends to show a recession postpartum, although the skin does not usually recover its original color [1].

Fig. 32.1 Hyperpigmentation in abdominal median line

The large population of melanocytes and susceptibility to the hormonal stimulus condition the hyperpigmentation to specific areas. Increased melanocyte-stimulating hormone (MSH), adrenocorticotropic hormone (ACTH), and estrogen levels during pregnancy have been implicated in the etiology of hyperpigmentation. However, the MSH serum level displays a late increase during pregnancy and does not decrease postnatally. The ACTH level increases when pregnancy starts and reaches four times its rate between the 7th and 10th week; it reverts to its usual concentration 24 h postpartum [2]. Estrogen and progesterone may be more related to hyperpigmentation, since progesterone levels show a persistent increase throughout pregnancy, whereas the estrogen levels tend to decrease over the later stages, from the 30th week on, a standard comparable with the clinical characteristic of pigmentation [1, 5].

Melasma is the main representative of local hyperpigmentation in pregnant women. It appears

in up to 75% of patients, mainly in the second gestational trimester, more often being seen in black women. It is characterized by facial irregular melanin pigmentation prevalent on the central facial block (63%), followed by the malar and the mandibular regions (less than 10%) [5, 7]. The facial central type shows pigmented forehead, cheeks, upper lip, and chin. Melasma is classified into epidermal (70%), dermal (10%), and mixed (20%), depending on the location of the melanin pigment [4].

Melasma etiology is multifactorial, possibly resulting from oral contraceptive use, genetic and racial factors, and sun exposure, among others [3, 4]. Increased levels of estrogen, progesterone, and MSH are probable etiologic factors [5].

Complete resolution of melasma usually is reached up to a year after childbirth, although around 30% of cases display evolution with some patchy sequelae. The presentation is usually recurrent in posterior pregnancies. In women who have used oral contraceptives, and in dermal melasmas the lesion is usually more persistent [1]. Therapeutic management during pregnancy and lactation is usually limited by a possible repercussion in the mother-fetus dyad. Treatment includes photoprotection, avoidance of strong sun exposure, and topical medication. Azelaic acid and topical nonfluorinated corticosteroids can be useful [7]. Corticosteroids have a depigmenting action by inhibiting the melanocytes, and azelaic acid acts as a competitive inhibitor of the tyrosinase. Formulas with corticosteroids, hydroquinone, and tretinoin can be used postpartum and provide partial or total improvement [1]. Patients must be well advised about the high relapse rate, and must continue to avoid sun exposure since there is no definitive treatment to date.

Recent scars, ephelides, and melanocytic nevi may display intensified pigmentation during pregnancy. The nevi have to be well assessed because new nevi may develop, enlarge, and/or become more pigmented [7], probably due to increased estrogen and progesterone. However, there are no conclusive research studies on the higher risk for malignant transformation [1].

The connective tissues go through hormone action via cortisol, relaxin, and estrogen, besides physical action by the gestational stretching of mammary and uterine tissues resulting in striae. *Striae*, very uncomfortable for pregnant women, may develop in up to 90% of women during the 6th and 7th gestational months [6]. Striae are more common in Caucasian women, possibly displaying a family trend, and they develop as opposed to skin tension lines through distension. They are more often found in the abdomen, breasts, arms, and torso (Fig. 32.2). There is a significant association between development of maternal striae and weight gain. The striae start with a rose-purple feature, and some months after childbirth they become pale, with no trend toward spontaneous resolution. Prevention of striae by oily massage remains controversial. Even if not totally receding, the striae may show great improvement by the end of pregnancy, and start showing a more tenuous pearly white feature. Post partum the striae can be treated with topical tretinoin, vitamin C, chemical peelings (serial
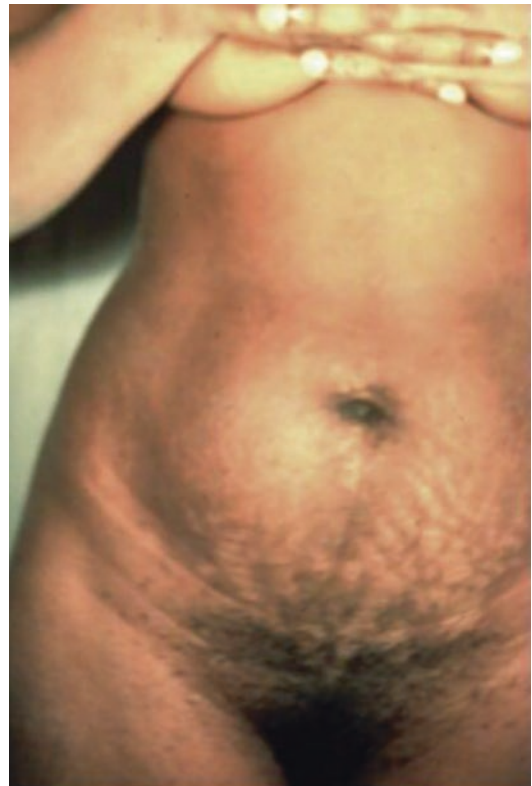
Fig. 32.2 Abdominal striae

retinoic acid), and microabrasion, with variable therapeutic response [1, 7].

The eruption of *multiple acrochordons* is frequently seen in pregnancy and located on the face, neck, trunk, and breasts. They probably develop as a result of increased insulin-like growth hormone. They can be seen throughout the late pregnancy phase and may spontaneously resolve postpartum [7].

Gland activity is directly changed through hormone alterations during pregnancy. The eccrine glands progressively increase their activity, resulting in a high incidence of *miliaria* and *dyshidrotic eczema* during this period. Paradoxically, there is a decrease of palmar sweating [1]. The apocrine glands decrease their activity along the course of gestation, and some disorders improve, such as hidradenitis suppurativa [1]. Sebaceous glands tend to display increased secretion in the third trimester. *Montgomery tubercles* on the areolas display increased development through hyperplasia of the sebaceous glands [6, 7].

Vascular changes are also prevalent during pregnancy, and are traditionally transient, showing late postpartum resolution [3]. They develop via proliferation of blood capillaries with increased hydrostatic pressure and reactivity, and distended blood vessel walls. These modifications are related to changes of the vascular tonus, apparently altered by estrogen and progesterone [7]. The following developments can be observed: spider nevus, palmar erythema, telangiectatic granuloma, hemangioma, hemangioendotheliomas, glomus tumors, varicosities, and postural edema of the lower limbs [7].

Vascular spiders are characterized by a central punctiform papule with irradiated telangiectasias that develop between the 2nd and 5th gestational months, more often seen in white women (67%) than in black women (11%) [6–8]. Vascular spiders are frequently noticed in the draining areas of the superior vena cava, such as the face, neck, and upper limbs, and their size tends to increase over months. High levels of estrogen seem to account for their origin. They usually disappear after the 7th week postpartum. Recurrence is possible during subsequent pregnancies. There is no need of specific therapy [1].

Palmar erythema is also often seen during pregnancy. It starts during the first trimester and more common in Caucasian women. Clinically, it may develop as an erythematous spotted pattern and impair the thenar and hypothenar regions or the palms, together with cyanosis and paleness [7]. It disappears in the first week postpartum. It is also related to high levels of estrogen besides increased volemia [1].

Varicosities impair more than 40% of pregnant women, more often found in the legs and anal region [5, 8]. They develop from the 3rd pregnancy month onward. They show a multifactorial etiology including family trend, frail elastic tissue, and increased venous pressure caused by uterine compression of the iliac vessels. They tend to recede postnatally, and prophylaxis can be used in the form of elastic stockings from light to heavy compression, use of appropriate low-heeled shoes, rest with elevation of the lower limbs or lying supine, together with a recommendation to avoid the orthostatic position for longer periods [5, 7, 9].

Small cavernous hemangiomas may develop in up to 5% of pregnant women, usually arising by the end of the first trimester [8]. Treatment is surgical for the persistent lesions, and as for the previously mentioned vascular changes, the cavernous hemangiomas may also be associated with estrogen levels.

Cutis marmorata on the legs are possibly a vasomotor impairment secondary to estrogen levels that may occur when patients are exposed to cold. It is characterized by a transient patchy cyanosis. If persisting after childbirth, its secondary causes must be investigated [8].

Peripheral edema is one of the most often seen lengthy manifestations in pregnant women. Its etiology includes sodium and water retention, besides circulatory changes resulting from the gravid uterus affecting circulation of the inferior vena cava [3].

Gravidarum granuloma, or pregnancy-associated pyogenic granuloma, is a very frequently seen gingival benign tumor, histologically not distinguishable from pyogenic granuloma. It arises as a gingival enanthematous wound, pedunculated or sessile, often associated with hyperplasia

of the periodontal tissue. Recurrence often happens by the end of pregnancy; therefore, it should not be inadvertently removed to avoid frequent recurrence. Strict oral hygiene is one of the factors that seem to prevent or avoid development of gestational pyogenic granuloma [5, 8, 10].

Regarding the mucosae, *gestational gingivitis* occurs in up to 100% of pregnant women and varies according to the impairment status. The usual onset is in the first trimester, with increasing severity up to the 9th month of pregnancy. It displays enlargement and enanthem of the interdental papillae, more intense in the lower incisor teeth [1]. Ulceration may occur. Its etiology seems to result from increased progesterone levels, poor oral hygiene, local irritating factors, and nutritional deficiencies. Treatment comprises local care. Orally administered vitamin C may be useful [8].

Hirsutism is another frequently seen finding in pregnant women, particularly those who already show abundant pilification before pregnancy. It is an early pregnancy finding, more often noticeable on the face and arms. Hirsutism etiology is probably hormonal and results from a decreased conversion of the anagen hairs into telogen hairs. It usually recedes up to 6 months after pregnancy, and there is no need for specific therapy [1].

Telogen effluvium is also common. Its onset occurs between the 1st and 5th month after delivery, lasting over many months. It results from the quick conversion of the anagen hair into telogen hair, secondary to unbalanced hormones and childbirth stress. Most patients display total recovery in about a year [5, 8].

The nails are also affected, possibly showing themselves as more fragile and brittle, with *transverse striae* (*Beau lines*), *distal onycholysis*, and *subungual keratosis* [7]. These ungual dystrophies disappear postnatally, only persisting in cases of trauma of the ungual matrix caused by frequent cuticle removal [1].

Finally, *pruritus* occurs in up to 20% of pregnant women; the onset occurs in the 3rd month and it intensifies over the gestational course [5]. It is more severe in the abdomen, and other dermatoses such as scabies, atopy, or neurodermatitis must be rejected. Treatment is symptomatic once the other diagnoses have been excluded [1].

Pregnancy-Altered Dermatoses

Throughout pregnancy, many pre-existing skin diseases are positively or negatively affected [16]. The immune reaction goes through a significant change during pregnancy. There is a decrease of the T-type helper-1 cells (Th1) in favor of the immune Th2 cells, decreasing the inflammatory activity [2]. This change happens during pregnancy and the initial postpartum phase, resulting in an important mechanism that alters autoimmune diseases. One example is exacerbation of systemic lupus erythematous in pregnancy that shows postnatal improvement, since it is a disease associated with a Th2 immune reaction. Psoriasis, in its turn, is a disease associated with the Th1 reaction that usually improves during pregnancy and worsens in the postpartum period [16].

Some allergic manifestations exacerbated during pregnancy are those of the *urticaria angioedema complex*, and these have to be monitored [43]. Regarding *atopic dermatitis*, its symptoms show large variation, from improvement to worsening, and pruritus is its cardinal sign [1].

Discoid lupus erythematous does not go through changes during pregnancy. In its systemic form, 60% of patients display cutaneous exacerbation throughout pregnancy, with a significant increased possibility of prematurity and abortion during disease activation. There is a higher pregnancy tolerance when the disease is in remission for at least 3 months before conception. In cases of primary diagnosis of *systemic lupus erythematosus* during pregnancy, the patient tends to display more severe manifestations [7]. The risk for neonatal lupus is rare, and is associated with the transplacental transmission of anti-Ro (SSA) antibodies, present in 30% of lupus patients, and in up to 60% of patients with Sjögren syndrome [7, 11]. Usually it is a self-limited disease that disappears after 6 months of the baby's life. The systemic treatment with corticoids and antimalarial drugs should not be interrupted [19, 20]. In these patients, the antiphospholipid antibody syndrome must be investigated.

Patients with *systemic sclerosis* or *scleroderma* may display improvement or worsening.

Worsening severity occurs in Raynaud's phenomenon, even with no disease change. Abortion and stillbirth may occur; nevertheless, 80% of pregnancies do not show complications during their evolution [7]. In *dermatopolymyositis*, there are cases of disease onset or exacerbation, with intensified skin and myopathic lesions, and reported improvement during pregnancy. Cases exist of postnatal occurrences of this disease. Perinatal morbidity and mortality is high, and prematurity is frequent [7, 11].

Antiphospholipid antibody syndrome includes the anticardiolipin antibody, and is clinically manifested by recurrent vascular thromboses, fetal losses, and prematurity resulting from eclampsia. Other findings include reticularis livedo (the most common cutaneous finding), cutaneous ulcerations, systemic arterial hypertension, thrombocytopenia, and hemolytic anemia. Therapy involves the use of acetylsalicylic acid and low-molecular-weight heparin [1, 7].

The various forms of *pemphigus* can be manifested or worsened during pregnancy. Exacerbations occur in the first or second trimesters in up to 40% of the patients, with increased fetal morbidity and mortality. Neonatal pemphigus is rare, with inconspicuous lesions that spontaneously recede over some weeks. The proposed mechanism is the passive transference of the mother's immunoglobulin G (IgG) through the placenta. The differential diagnosis with gestational pemphigus is important, and may be made through clinical particularities and direct immunofluorescence. Therapy during pregnancy includes the systemic corticosteroids (cytotoxic drugs must be avoided) [19].

Psoriasis is a disease that impairs many women in their fertile period because its peak occurs during adolescence and the third to fourth decades of life. Patients mostly display improved disease evolution during pregnancy, and immediate postpartum exacerbation. Regarding junction impairment, pregnancy may represent a trigger device. This clinical improvement may be noticed in posterior pregnancies. Treatment is controversial, mainly owing to the lack of conclusive research studies. Topical corticosteroids are classified as gesta-

tional risk C (with changes in animals, although there are no studies on human beings), with risk-benefit associated use. High-dose vitamin D products change the calcium and phosphorus levels. Cyclosporine has been reported to be associated with premature delivery, late fetal growth, and arterial hypertension, despite not being regarded as teratogenic or mutagenic. PUVA therapy (psoralen with ultraviolet A) must be avoided because of its teratogenic potential, as well as methotrexate. Phototherapy with narrow-band ultraviolet B rays can be used with appropriate safety and control. Systemic retinoids are contraindicated. Biological agents, in their turn, should not be indicated at this phase, although there are no reported complications of their use [11].

Some *cutaneous tumors* undergo alterations during pregnancy. Fibromas and keloids may show fast growth, as well as dermatofibrosarcoma, plexiform neuromas, and dermoid tumors [7]. The suspicious influence of pregnancy on the harmful course of the malignant melanoma is not defined in the literature, since the genesis of the outcome of hormone alterations is still controversial. Melanoma prognosis in pregnant women depends directly on the tumor thickness during the diagnosis, the same happening with patients in general. Reports of fetal metastasis already exist, and the avoidance of pregnancy for at least 2 years after tumor exeresis is recommended [19]. Most often the diagnosis and therapeutics of melanoma in pregnant women are delayed, thus leading to a worse diagnosis and a difficult treatment because of the impossibility of using cytotoxic drugs [16].

Porphyria cutanea tarda is usually aggravated in the first trimester of pregnancy because of increased estrogen level and porphyria excretion, although there are reported cases of attenuation of the disease course. There are no changes in the concept.

Pregnancy-Specific Dermatoses

Pregnancy-specific dermatoses are a heterogeneous group of inflammatory pruritic disturbances exclusively associated with pregnancy

and/or the puerperium. Over the decades they represented a disoriented group of overlaying entities known by personal comments and some case reports. Their terminology and classification were always very controversial because of the rarity of these diseases; the variation in their clinical morphology, the lack of efficient diagnostic examinations, and the limited treatment options.

Besnie, in 1904, included all patients with pregnancy-related dermatoses as gestational prurigo. Nurse, in 1968, divided the patients into early and late pregnancy eruptions. The late papular/urticarial form superimposed Bourne's "pregnancy toxemic eruption" (1962), and from this time on it has been described as pregnancy urticarial/pruritic papules and plaques [30]. Black and Holmes, in 1982, for the first time formulated a simplified classification of pregnancy-specific dermatoses. It comprised three groups: gestational pemphigoid, pregnancy polymorphic eruption, and pregnancy prurigo [12, 22]. One year later they added one more dermatosis, the pruritic folliculitis of pregnancy, a variation of the pregnancy prurigo [13, 14].

In 1998, Shornick altered Black and Holmes' classification [15]. In his research studies he showed that the pruritic folliculitis of pregnancy was a form of pregnancy prurigo. He included the pregnancy intrahepatic cholestasis to classify specific dermatoses. Owing to the lack of a primary wound, this disease had not been previously mentioned in the classification. Its identification in a pregnant woman with generalized abrasions or even vulgar prurigo is difficult. This disease is very significant since its diagnosis is differential, with great potential for fetal risk if neglected or not diagnosed early [16].

In 2006, Ambros-Rudolph et al. proposed a new classification after a research study with more than 500 pregnant patients with pruritus [17]. Thus, besides gestational pemphigoid, polymorphic eruption of pregnancy, and intrahepatic cholestasis of pregnancy, they included the term atopic eruption of pregnancy. They were able to show conspicuous overlaps in the clinical and histologic presentation in atopic dermatitis, gestational prurigo, and pruritic folliculitis of pregnancy in pregnant patients [16, 17].

Traditionally the polymorphic eruption of pregnancy was seen as the most frequent gestational dermatosis. After this last change, however, with the introduction of atopic dermatitis of pregnancy, it has represented 50% of all cases.

Gestational Pemphigoid

Epidemiology
Gestational pemphigoid ("gestational herpes"), is a bullous, autoimmune, rare, and self-limited disease during pregnancy. It is the best characterized dermatosis and the only one that can impair the newborn skin.

Its incidence varies from 1:7000 to 1:50,000 pregnancies. There are reports in the literature of its rare association with hydatidiform mole, choriocarcinoma, and oral contraceptive use. There is also increased risk for the development of other autoimmune diseases, especially Graves' disease [18].

Etiopathogenesis
Tissue damage results from stores of immune complexes in the basal membrane zone (BMZ), with later activation of the complement and intense migration of eosinophils [1].

It has an autoimmune etiology and corresponds to the production of complement-fixing antibodies of the IgG1 subclass directed against a hemidesmosome 180 kDa transmembrane protein (BPAG2; collagen XVII). Subsequently, the traditional complement is activated via the lesion at the dermal epidermal junction level and development of a subepidermal blister. The mechanism that accounts for the beginning of antibody production is still unknown [44]. Immunogenetic research studies made evident a potential cross-reactivity between the placenta tissue and the skin. This possibly explains the disease onset in the periumbilical region. Furthermore, the association with the hydatidiform mole, contraceptive use, menses, and other factors raises the strong possibility of hormonal influences on the presentation [26]. The explanation may lie in an immunologic reaction against the aberrant expression of the class II MHC molecule, probably from the father, in the

placenta, and the later cross-reaction with the cutaneous epithelium. In a study of 25 gestational pemphigoid patients, Holmes et al. noticed increased human leukocyte antigen (HLA) DR3 (60–80%) and HLA DR4 (50%) antigens, or both forms (40–50%) [23, 24]. There is an incidence of 100% anti-HLA antibodies in patients with a history of gestational pemphigoid [23, 44]. Women showing this cutaneous impairment seem to be more susceptible to many autoimmune diseases, particularly Graves' disease [25].

Up to 75% of patients display the IgG1 antibody that binds the complement to the serum. C3 prevalence in the basal membrane and the presence of eosinophils suggest that complement activation and eosinophil chemotaxis are extremely significant for tissue damage [20]. Regarding the bullous pemphigus, complement activation is not the main factor in this disease pathogenesis.

The antigen in gestational pemphigoid is a 180 kDa transmembrane protein codified by the long arm of the tenth chromosome [26]. It is different from the 230 kDa intracellular protein of the bullous pemphigoid, codified in chromosome 6. Among other reasons, this is why many authors still favor the term gestational herpes, thus highlighting the differences from bullous pemphigoid, even with no viral etiology for the disease.

Up to 10% of newborns display lesions similar to their mothers', although they disappear without sequelae. Even healthy newborns may present complement or IgG stores in the BMZ [1].

There is an increased trend of low-weight newborns and prematurity after episodes of gestational pemphigoid, although no morbidity or mortality has been confirmed thus far [25, 27, 28].

Clinical Presentation

Clinically, gestational pemphigoid occurs more often in the second and third gestational trimesters and beginning of the puerperium, although it may be seen at any gestational phase. It may develop in the first pregnancy or in subsequent pregnancies. If it develops after a previous presentation, it tends to be earlier and more severe [13, 19]. Nevertheless, subsequent pregnancies are not always impaired, a fact that may result

from paternal alteration or higher compatibility of the fetus-mother HLA [1].

At first, there are papules and urticariform plaques with severe pruritus [20]. The urticariform lesions may be annular or polycyclic, followed by vesicles and blisters (Figs. 32.3 and 32.4). In 81% of the cases the early lesions are periumbilical, followed by trunk, limbs, palms, and soles impairment (Fig. 32.5). The face and the oral mucosa are generally spared [13].
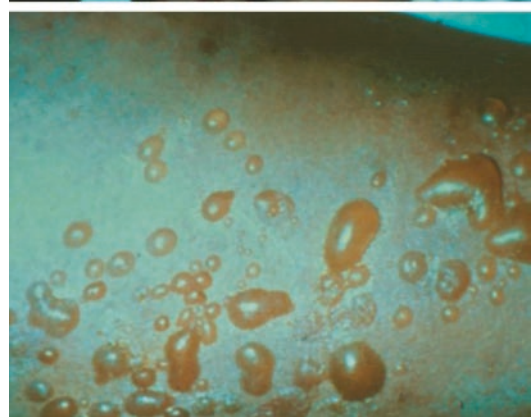
Figs. 32.3 and 32.4 Bullous lesions of gestational pemphigoid

Fig. 32.5 Periumbilical lesions of gestational pemphigoid

Blisters and vesicles often split, and erosion and crust development are noticed. The vesicular arrangement may be reminiscent of herpetic infection (earlier known as gestational herpes), whereas the tense blisters evoke bullous pemphigoid or bullous lupus.

In general, the wounds resolve in up to 6 weeks postnatally [13], although there are reports of patients who displayed new wounds up to 10 years after pregnancy. As a rule, there is remission of the presentation by the end of pregnancy, followed by a postpartum acute phase in 75% of the cases. In the puerperium, gestational pemphigoid intensification is common, although new blister development 3 days after delivery must raise suspicion of another diagnosis [1]. After the apparent resolution of the presentation, exacerbations may occur during menses or when contraceptives are used [1].

Complementary Examinations
The histopathologic examination varies according to the disease stage and severity. Edema is noticed at first on the papillary dermis, with

inflammatory infiltrate made up by lymphocytes, eosinophils, and some neutrophils. The developed blister is subepidermal and has many eosinophils.

Direct immunofluorescence, regarded as the gold standard for the diagnosis, reveals linear stores of C3 in the basal membrane. IgG deposits in the BMZ are found in 25% of cases. Holubar, however, suggested that this is a reflection of a slight lack of technical sensitivity, since the existence of IgG stores was verified through immunoelectron microscopy in a negative immunofluorescence patient [21].

Laboratory tests show increased inflammatory markers and peripheral eosinophilia. Antinuclear antibodies and complementary doses do not display changes.

Therapeutic Approach
Gestational pemphigoid treatment must initially be conducted with oral antihistamines and topical corticosteroids. If there is no reaction, start oral corticosteroids at doses up to 0.5–1 mg/kg/day, possibly reaching larger doses. As soon as new blister development is suppressed, prednisone must be started with a slow decrease in dose [29]. However, high corticosteroid doses may increase the risk for premature membrane rupture, postterm delivery, late intrauterine growth, and maternal side effects. Plasmapheresis may be an option in extreme cases.

Pregnancy Polymorphic Eruption

Epidemiology
A gestational dermatosis is common, with an incidence of 1:160 pregnancies [31, 32]. It is an inflammatory, benign, self-limited, pruritic disease that usually occurs in the third gestational trimester or the early puerperium [30, 31]. Initially called pruritic urticarial papules and plaques of pregnancy or PUPPP, it is associated with first-time mothers (80%), twin pregnancy, and exaggerated weight gain in pregnancy, with neither postnatal worsening nor a recurrent trend in subsequent pregnancies [34, 45]. It lasts around 6 weeks while

the pruritus worsens gradually, afterward tending toward a spontaneous resolution.

Etiopathogenesis

The cause of polymorphic eruption in pregnancy is not yet established. The main proposed theories are related to excessive abdominal distension, and hormonal and immunologic factors [34]. Initially, the lesions develop inside the striae when pregnancy distension is more severe, associated with the mother's excessive weight gain, maternal obesity, or multiple pregnancies. Therefore, there exists the hypothetical suggestion that the rapid distension of the abdominal wall of first-time mothers possibly brings about damage to the connective tissue and later inflammatory reaction. There is an increase of CD1 cells in the inflammatory infiltrate, which possibly acknowledges the theory that the previously motionless structures develop an antigenic character, resulting in triggering of dermatosis [31, 33].

Clinical Presentation

It clinically manifests as very pruritic urticariform papules initially on the abdominal striae, sparing the periumbilical region and spreading to the thighs, gluteal region, and arms (Fig. 32.6). The papules usually appear during the end of the third trimester (85%) or in the immediate postpartum period (15%) [31]. Subsequently they
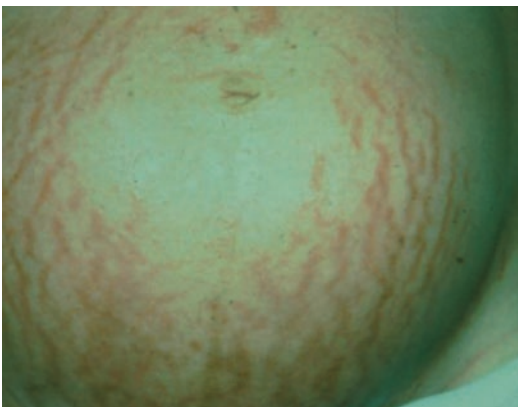
Fig. 32.6 Lesions of the pregnancy polymorphic eruption spreading on the striae, thus sparing the periumbilical region

may coalesce into plaques and spread over the body, sparing the face, palms, and soles. Eruption may become polymorphic, with vesicles (15%), target lesions (5%), and polycyclic lesions (5%) [31]. In general, the lesions recede in up to 6 weeks with scaling and crusts during the resolution phase [32]. The differential diagnosis includes gestational pemphigoid, scabies, contact dermatitis, and multiform erythema.

The newborn skin is not affected by pregnancy polymorphic eruption, and there is no maternal morbidity. Recurrences are not frequent except in cases of multiple subsequent pregnancies.

Complementary Examinations

Histology is unspecific and varies according to the disease stage, from light spongiosis to acanthosis with hyperkeratosis and parakeratosis. Edema is noticed on the superficial dermis, besides spongiosis with eosinophilic infiltrate during the urticariform phase. Regarding the vesicular phase, intense spongiosis and subepidermal vesiculation are seen. Finally, during the resolution phase, parakeratosis and acanthosis are prevalent. Routine laboratory assessment is normal, and direct and indirect immunofluorescence are essentially negative in this dermatosis [32].

Therapeutic Approach

The majority of pregnant women benefit from symptomatic treatment only, with antihistamines and topical corticosteroids, since it is a self-limited disease with no risks either the mother or fetus, and spontaneous resolution [31]. In more severe presentations, systemic corticosteroid therapy may be used with a brief healing period that is usually very efficient [32].

Intrahepatic Cholestasis of Pregnancy

Epidemiology

Intrahepatic cholestasis of pregnancy is a reversible gestation-specific form of cholestasis that typically occurs in the end of the second trimester. It shows a varied incidence according to

location and ethnicity. It is less frequent in Europe and North America (0.1–1.5% of pregnancies), and is more often seen in Chile and Bolivia (9–16%) and Scandinavia (1–2%) [35, 37, 45, 46]. In contrast with the other pregnancy dermatoses, intrahepatic cholestasis displays pruritus and skin lesions exclusively secondary, mainly attributable to the act of scratching. Intrahepatic cholestasis in pregnancy occurs in some families under genetic influence (50%) [35, 36, 37]. Most of the time (70%) it develops in the second trimester of pregnancy in women older than 35 years with multiple pregnancies, possibly suggesting a relationship with higher hormone levels (e.g., estrogen), and in women with a history of cholestasis in previous pregnancies. The recurrence rate varies from 40% to 60% of pregnancies, greatly varying with regard to disease severity in posterior pregnancies, and also occurring in patients who use oral contraceptives, mainly those with high estrogen doses.

Etiopathogenesis

Etiopathogenesis is based on the decreased excretion of biliary salts and increased serum levels, resulting in severe pruritus in the mother and damaging effects in the fetus. These increased biliary acids cross the placental barrier probably resulting in abnormal uterine contractility, chorionic vein vasoconstriction, and fetal hypoxia [37]. In families with intrahepatic cholestasis, gene mutation that codify the carrier proteins necessary for biliary excretion (e.g., ABCB4 gene)s were noticed, thus acknowledging the genetic influence [45]. Other contributing factors are the cholestatic effect of progesterone and estrogen metabolites, and infection by the hepatitis C virus. There is also influence of nutritional factors, such as selenium deficiency and increased intestinal permeability.

Clinical Presentation

Intrahepatic cholestasis of pregnancy usually begins with a sudden onset of severe pruritus that may start on the palms and soles of feet, rapidly spreading. It persists throughout pregnancy and can be very severe. The pruritus remains up to the time of delivery and resolves in a few days; per-

sistent cases are rare and other hepatic diseases, such as primary biliary cirrhosis, must be ruled out. The clinical characteristics are related to the disease duration [37]. Primary lesions are not seen, and secondary lesions occur as a result of scratches and abrasions, possibly evolving into severe pruritic nodules with persistent pruritus. The cutaneous lesions usually evolve to the extensor limb surfaces, although they can also affect other body sites, such as the gluteal region and abdomen. Jaundice is not common and occurs in about 10% of patients, usually 2–4 weeks after the disease onset. These diseased individuals have a risk for developing steatorrhea, with a poor absorption of liposoluble vitamins, including vitamin K, and potential hemorrhagic complications, as well as cholelithiasis [35].

Maternal prognosis is usually satisfactory. After delivery, the clinical presentation spontaneously resolves [35]. Presentations with jaundice or vitamin K deficiency display a higher risk for hemorrhage and biliary calculi. However, the crucial situation in this disease is not the maternal pruritus but the fetal complications. Intrahepatic cholestasis of pregnancy is associated with a higher risk for prematurity (19–60%), fetal distress (22–33%), and stillbirths (1–2%), which correlate with higher biliary acid levels, particularly if higher than 40 μmol/l [35, 40]. Rapid diagnosis, specific treatment, and close obstetric follow-up are crucial.

Complementary Examinations

The histologic findings are unspecific, and direct immunofluorescence is negative. The usually detected laboratory changes include increased plasmatic levels of serum biliary acids, predominantly cholic acid, and hepatic transaminases, possibly reaching values twice higher than the normal values; and increased plasmatic levels of bilirubins, mainly direct bilirubin, given that this parameter is regarded as the most predictive of the disease, although normal levels of biliary acids do not rule it out. The biliary acid levels correlate with pruritus severity. In healthy pregnancies, the total levels of biliary acids are slightly higher than in nonpregnant women,

and levels up to 11.0 μmol/l (normal interval, 0–6 μmol/l) are accepted as normal by the end of pregnancy [38–40]. Liver ultrasonography may be necessary to rule out cholelithiasis in patients with abdominal symptoms and/or hyperbilirubinemia.

Therapeutic Approach

The aim of treatment aim serum decrease of the biliary acids to lengthen the pregnancy and reduce the fetal risks and maternal symptoms. Ursodeoxycholic acid (UDCA) is the only effective treatment, considered a first-line treatment to decrease maternal pruritus and improve the fetal prognosis [37, 41, 42]. In intrahepatic cholestasis of pregnancy, a 15 mg/kg daily dose, or, disregarding the body weight, a 1 g daily dose, is administered as the only dose, or divided into two to three doses until delivery, when administration can be interrupted. This is usually well tolerated, with only a few reports of light diarrhea. However, UDCA has not yet received approval for use during pregnancy; therefore, it requires express directions to the patient regarding its special use ("off-label use"). Antihistamine drugs, including S-adenosyl-L-methionine, dexamethasone, and cholestyramine, do not improve the fetus' prognosis. Cholestyramine and other biliary acid exchange resins may have a role in the poor absorption of vitamin K and possible hemorrhagic complications; therefore, their use must be avoided. Besides UDCA treatment, a close obstetric surveillance (fetal cardiotocography from the 34th gestational week), and induced delivery are indications, as soon as fetal lung maturity is accomplished (36th to 37th weeks), in severe cases. An interdisciplinary approach to intrahepatic cholestasis of pregnancy by dermatologists, hepatologists, gynecologists, and pediatricians is mandatory.

Atopic Eruption of Pregnancy

Epidemiology

Atopic eruption of pregnancy is the most often seen pruritic disease in pregnant women, and has shown a trend to develop earlier than the other gestational dermatoses. Its incidence is unknown, although high. It is a benign pruritic pregnancy-specific disease, defined as an exacerbation or a first manifestation of eczemas and/or papular lesions in patients with atopic background, after ruling out other diseases. It accounts for 50% of gestational dermatoses, and has an early onset, before the third trimester, in about 75% of cases. It has a recurrent tendency regarding subsequent pregnancies if the atopic context is considered.

Etiopathogenesis

An immunologic gestational physiologic change occurs, with decreased cell immunity and humoral increase in order to avoid fetal rejection. It is believed that this dermatosis is triggered by the following immune changes: decreased cell immunity and reduced Th1 cytokine production (interleukin (IL)-2, interferon-γ, IL-12), which is in contrast to the dominant humoral immunity and increase of Th2 (IL-4, IL-10) cytokine secretion. This favors a dominant Th2 response that changes the balance of most atopic patients, thus making easier the development of atopic eruption of pregnancy [17].

Clinical Presentation

The clinical presentation is variable. About 20% of patients undergo an exacerbation of the pre-existing atopic dermatitis, with a typical clinical presentation. The remaining 80% patients display primary atopic manifestations or reactivation after a long remission (e.g., since childhood). Of these patients, two-thirds show eczematous generalized manifestations, often affecting the traditional atopic sites such as the face, neck, and flexor surfaces of the limbs, whereas one-third displays papular lesions that vary from small erythematous papules disseminated throughout the trunk and limbs to typical pruritic nodules, mostly located on the limbs (Figs. 32.7 and 32.8). The maternal prognosis is good even in extensive cases; recurrence in subsequent pregnancies is common. Fetal risk is absent.

Complementary Examinations

The histologic features may show variation depending on the lesion stage. Acanthosis, spongiosis, and

**Figs. 32.7 and
32.8** Atopic eczema

erosions may be seen on the epidermis; lympho-cyte and eosinophil infiltrate may be seen on the dermis. There may be sterile follicular inflamma-tion. Direct immunofluorescence is negative. Laboratory tests can reveal increased levels of serum IgE in 20–70% of cases [17].

Therapeutic Approach

The implemented topical treatments include emollients that may have urea, and antipruritic additives, such as menthol and polidocanol, regarded as safe substances for pregnant women. Skin dryness may be prevented with the use of light nonalkaline synthetic detergents and bath oils. The controlled use of topical corticosteroids may be prescribed. Potent corticosteroids must be avoided. Ultraviolet B irradiation is very use-ful and safe in severe diseases.

If treatment with systemic corticosteroids is necessary, prednisone is the agent of choice dur-ing pregnancy. The usual initial dose is 0.5–2 mg/kg daily, depending on the disease nature and severity. The maintenance dose should not exceed 10–15 mg daily in the first trimester because of possible teratogenic effects. For the treatment of gestational dermatoses, corticosteroids are usu-ally used as a short-term therapy only (<4 weeks). Antihistamines may also be necessary for symp-tom control.

Glossary

Dermatosis   Any disease of the skin.
Eczema   An inflammatory condition of the skin attended with itching and the exudation of serous matter.
Histocompatibility   The condition of having antigenic similarities such that cells or tissues transplanted from one (the donor) to another (the recipient) are not rejected.
Immune complex   Aggregate of an antigen and its specific antibody.
Microabrasion   Technique used in remov-ing surface stains, using abrasive or erosive substances.

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Neonatal Dermatosis

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Ana Elisa Kiszewski

Key Points Summary

- Almost all newborns present some transient neonatal dermatosis or birthmarks
- The most prevalent transient dermatoses are milia, sebaceous gland hyperplasia, and toxic erythema
- The most prevalent birthmarks are Mongolian spots and salmon patch
- Detecting neonatal dermatoses is important because it allows parents to make adequate decisions regarding treatment
- Environmental and ethnic factors may significantly influence some neonatal transient dermatosis and birthmarks
- Some neonatal dermatoses are present in the first day of life, whereas others appear in the first weeks of life; this may justify, in part, the variation in frequency of these dermatoses found among different studies

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Introduction

Directly after birth, the neonatal skin presents particular characteristics that help the transition from the fluid intrauterine environment to the gaseous and dry environment in which we live. The skin is essential for mechanical and immunologic protection, thermoregulation, and maintenance of a barrier that prevents loss of body fluids. Almost all newborns present some physiologic alteration, transient skin lesion, or birthmarks [1]. When examining oral mucosa and skin, the incidence of transient skin lesions may reach 99.3% [2]. Skin lesions are variable; they may result from a temporary physiologic reaction or may represent potentially serious dermatosis or a temporary or permanent skin spot [3]. Detecting neonatal dermatosis is important because it allows parents to make adequate decisions regarding treatment, if needed. Didactically, it is possible to classify neonatal dermatoses into the following categories:

Transient: Physiologic desquamation, vernix caseosa, suction blister, physiologic cutis marmorata, harlequin color, generalized redness, lanuginosa hypertrichosis, mini puberty, mucous cyst (Epstein pearls and Bohn nodules), milia, miliaria, sebaceous gland hyperplasia, suction blister, toxic erythema, neonatal acne, neonatal cephalic pustulosis, infantile acropustulosis.

Birthmarks: Pigmented: Mongolian spots, café-au-lait spots, congenital melanocytic nevus; vascular: salmon patch, congenital hemangioma (rapidly involuting and noninvoluting congenital hemangiomas), infantile hemangioma (precursor lesion), capillary vascular malformation (port-wine stain).

Several prospective studies performed in different continents (Americas, Europe, Asia, and Oceania) investigated the incidence of dermatosis in newborns. Despite the considerable variation observed among countries, the most prevalent transient dermatoses were milia, sebaceous gland hyperplasia, and toxic erythema. Among birthmarks, Mongolian spots and salmon patch were the most prevalent. When taking into account ethnic factors, studies indicated that Mongolian spots, genital hyperpigmentation, and transient neonatal pustular melanosis (TNPM) were more frequent in Africans. On the other hand, palatine cyst, salmon patch, and toxic erythema were more prevalent in Caucasians [1, 2, 4]. Furthermore, when taking into account environmental factors, a greater number of newborns with miliaria were found in countries where high temperatures are predominant, whereas newborns exposed to lower temperatures have greater frequency of acrocyanosis and physiologic cutis marmorata [5].

Physiologic Aspects of Newborn Skin

The newborn presents at birth a skin structure similar to that of an adult; it is divided into three layers (epidermis, dermis, and subcutaneous cellular tissue) and already presents cutaneous annexes. However, the dermis is thinner (40–60% less than that of an adult), the dermo-epidermal junction is more fragile, and the collagen fibers are smaller. The vascular and nervous structures are immature, and the sweat glands only become functional from the third week of life owing to the newborn's immature autonomic nervous system. Sebaceous secretion increases during the first month of life, since the gland is stimulated through the

mother's hormones [3, 6, 7]. In addition, the lower the gestational age, the greater the immaturity of the skin barrier, resulting in greater transepidermal water loss, greater permeability, and higher risk of absorption of substances applied over the skin [6].

The newborn's skin is sterile at birth; however, directly after birth it becomes colonized by coagulase-negative *Staphylococcus*, in particular *Staphylococcus epidermidis*. Other genera such as *Micrococcus*, *Peptococcus*, *Coryneobacterium*, *Propiniobacterium*, and *Streptococcus* will later become part of the resident microbiota, appearing gradually weeks after birth. The average skin pH at birth is 6.34; however, after a few days this decreases to 4.95 [6, 8]. Maintenance of an acidic skin pH is part of the defense system of the body to prevent the penetration of microorganisms. Most newborns remain at the hospital for only a short period and therefore do not acquire nosocomial microbiota. Nevertheless, newborns who are hospitalized, in particular those in the intensive care unit, may become colonized by pathogenic bacteria such as *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Serratia* spp., and *Acinetobacter* spp. [6 , 8].

Dermatosis

Vernix Caseosa

Vernix caseosa is a biofilm synthesized by the newborn during the last quarter of gestation and covers most of the body surface directly after birth. It is a white, greasy substance comprising epithelial cells, sebum, and sometimes lanugo. In the intrauterine environment, vernix forms a protective barrier for the fetus against the maceration effect of the amniotic fluid, in addition to having antibacterial function. The lubrication function of vernix is very important because it facilitates the passage of the fetus through the birth canal. In addition, after birth it functions in the thermal control of the newborn [3]. Vernix color may reflect a potential intrauterine problem, with brownish yellow color being

frequent in post-term babies and greenish color being associated with fetal distress or hemolytic disease. Vernix may be colonized by bacteria during intrauterine infections, in which case it acquires a characteristic foul smell, which is a symptom of neonatal sepsis. Meconium is a secretion produced by fetal intestine, and when excreted in the amniotic fluid may be a sign of fetal distress. Meconium has a dark green color and may impregnate the vernix, skin, nails, and the umbilical cord [6, 7]. In a study carried out in India, vernix caseosa was found in 92.8% of full-term newborns, 5.9% in preterm newborns, and 1.5% in post-term newborns [9].

Physiologic Desquamation

Physiologic desquamation is a thin, furfuraceous desquamation, observed with greater frequency on the hands and feet during the first 2 weeks of life. The frequency of physiologic desquamation is greater between the 40th and 42nd weeks of gestation [6]. Few studies have evaluated the incidence of physiologic desquamation in newborns [1]. Haveri and Inamadar [9] observed that physiologic desquamation was present in 92.3% of full-term newborns, 4.7% in preterm newborns, and 2.88% in post-term newborns. Other studies showed that the frequency of physiologic desquamation varied between 40% and 65% of neonates in India and Australia, respectively [2, 5]. Zagne and Fernandes [10] found that physiologic desquamation was more prevalent in newborns born through cesarean section (24.7%, $p < 0.05$). They also reported that newborns presenting with a greater amount of vernix caseosa at birth were subsequently predisposed to greater desquamation.

Generalized Redness and Acrocyanosis

Redness and acrocyanosis in newborns are physiologic findings that represent vasomotor instability. The redness is persistent hyperemia in the first hours or days of life and reflects peripheral vasodilation in addition to excess circulating hemoglobin. It tends to disappear along with the physiologic decrease in hemoglobin levels [3, 7]. The extremities (hands and feet) may present with a bluish color when the baby cries, breastfeeds, or feels cold, a phenomenon called acrocyanosis. This phenomenon appears to be associated with the increase in tonus of peripheral arterioles, which produces arteriolar vasoconstriction with secondary dilation of the venous vessels [8].

Physiologic Cutis Marmorata

Cutis marmorata is a phenomenon that occurs with greater frequency in newborns with fair skin [10]. It is characterized by the presence of reticulated, erythematous, violet-colored skin that affects the upper body and extremities of the newborn when he or she is cold. The phenomenon has no pathologic significance and disappears quickly when the baby is warmed. In some patients with more exuberant and persistent lesions, differential diagnosis should be performed for cutis marmorata telangiectatica congenita, and capillary vascular malformation [3].

Lanugo

Lanugo is thin hair with little pigmentation and without medulla. Before birth the fetus is covered with lanugo, which usually appears during the second quarter of gestation and may be seen in preterm babies [6]. This lanugo falls during the third quarter of gestation and is replaced by shorter lanugo, still during the intrauterine period, and may cover most of the newborn's body. Lanugo is more frequent in non-Caucasian newborns, and the most common locations are the face, shoulders, posterior trunk, auricular pavilions and scalp [3, 6, 8]. After birth, the first synchronized shedding of lanugo starts after the second week of life and lasts until the third month, beginning on the frontoparietal region and ending on the occipital region. Lanugo hair will be replaced by vellus hair, in the body, while terminal hair will grow from the

scalp. After the third month of life lanugo on the scalp will be replaced by vellus and terminal hair, which lengthens and falls between 12 and 24 months of life, and after this shedding, most of hair will be terminal in the scalp. During the first year of life occurs the transitioning from a synchronized shedding model to a model in which each follicle has its own rhythm [6]. Most studies do not mention the frequency of presence of lanugo in newborns. In two studies, this frequency varied from 25.7% to 35.3% [9, 11].

Mini Puberty

Mini puberty results from the hormonal transference of mother's hormones to the newborn through the placenta [7], and occurs in both male and female newborns. It includes hyperpigmentation of the genitals and the medium line and increased mammary turgescence in male and female infants; sometimes it includes lactic secretion, popularly known as "witch milk." The mammary ingurgitation decreases at the end of the second week of life and tends to disappear in the first month; it is discreet or absent in preterm newborns. The action of testosterone on the skin may result in hyperplasia and increased secretion of sebaceous glands, similar to what occurs in puberty. In girls the genitals become edematous, the clitoris may be increased in size and enclosed, and vaginal discharge may occur (which may be mucoid or a mucus-bloody discharge). In boys the testicles are also increased in size [8]. Two studies performed in India found a frequency of 5.6–13.3% in newborns [5, 9].

"Harlequin" Color

Harlequin color refers to the different hemicorporal color in newborns, secondary to a vascular phenomenon, resembling harlequin clothes. It results from a transient deficiency in the central regulation of the peripheral vascular tone (vasomotor immaturity). Erythema (vasodilation) occurs on the side on which the baby is lying, and pallor (vasoconstriction) occurs on the other side of the body [6, 7]. The face and genitals are not affected. The harlequin color may last a few seconds or minutes (20 min or more) and disappears after changing the position or warming the body of the newborn [3]. This vascular phenomenon does not present a risk to newborns, usually disappearing after the third week of life. It is estimated to occur in 0.4–15% of newborns; however, there is a lack of studies that assess this characteristic [7, 9].

Suction Blisters

These are blisters with serous content (surrounded by normal skin), erosions, or scabs up to 2 cm in diameter that may be present at birth or subsequently, and are due to vigorous oral suction by newborns on a site [3, 12]. The prevalence has not yet been defined, but two studies detected blisters caused by suction in 1% and 9.8% of newborns in Brazil and Australia, respectively [2, 10]. The blisters are located on the radial side of the forearms, fists, hands, fingers, or any other part of the body that the baby's mouth can reach. It resolves spontaneously and without sequelae [3, 8]. The use of topical antibiotics on erosions is recommended to avoid secondary infections [8, 12].

Gingival and Palatine Epidermal Cyst

As many studies on the prevalence of dermatoses in newborns do not focus on the oral cavity, the frequency among different populations is unknown. Some studies have detected gingival and palatine epidermal cysts in 61–64% of newborns [1, 3, 5]. These are benign cysts considered to originate during epidermal enclosure. They are called Epstein pearls or papules when they form in the transition between the hard and soft palate, on the midline [10]. The frequency of Epstein pearls varies from 54% to 89% [1, 9, 11]. These are single or multiple yellowish white papules, varying from 1 to 2 mm in diameter. They are considered the equivalent of milia mucosa and are called Bohn nodules when the cysts are located in the gums [3, 6].

Milia

Milia are white, millimeter-sized cysts (1–2 mm) found mainly on the face and scalp of newborns, and may exist as single or multiple cysts [12]. The areas most affected are the nose, cheeks, mentum, and forehead. In most cases the lesions disappear spontaneously after the first month of life but in some infants may remain until the third month of life. Histologically, milia comprise cysts of epidermal enclosure at the infundibulum of the pilosebaceous follicle and contain many concentric layers of keratinized stratum corneum. Treatment is not required because milia usually disappear spontaneously in the first months of life [3]. Incidence varies, with 7.5% in Iran, 8% in the United States, and 86% in Australia [3, 9, 11].

Miliaria

Miliaria is a common dermatosis during the neonatal period and may manifest as miliaria rubra or crystallina (Fig. 33.1). It is caused by the obstruction of the excretory duct of the eccrine sudoriferous glands, which may lead to the rupture of the ducts [13]. It occurs more frequently in children born in countries with tropical weather [6, 12]. In a study from India, miliaria crystallina was present in 3% of newborns, 76.6% of whom were full-term infants [9]. Miliaria was present in 1.3% of newborns in Iran [11] and in 2% of newborns in Brazil

Fig. 33.1 Miliaria

[10]. Clinically, miliaria rubra is characterized by multiple erythematous papules, with punctiform shape, in regions with greater concentration of eccrine sudoriferous glands as well as intertriginous areas such as the scalp, face, and upper body [12]. In miliaria crystallina, the lesions resemble water droplets on the skin; they burst easily and comprise sweat droplets trapped in the corneal layer [13]. From the histopathologic viewpoint, miliaria rubra shows spongiosis and formation of vesicles inside the eccrine duct, whereas miliaria crystallina shows intracorneal and subcorneal vesicles [12].

Hyperplasia of Sebaceous Glands

This dermatosis comprises yellowish papules that result from the dilation of sebaceous glands in the cheeks and nasal, frontal, and perioral regions. It tends to recede spontaneously in the first weeks of life [6]. The relation between these lesions and gestational age, sex, or ethnic group remains unclear. Hyperplasia of sebaceous glands is frequently associated with milia. Sebaceous hyperplasia occurs during the last month of gestation, as a result of the stimulation of the pilosebaceous follicles by maternal androgens, resulting in an increase in the number and volume of sebaceous glands. From the epidemiologic viewpoint, its frequency varies among studies, with reports of 30% of newborns in India, 42.6% newborns in the United States, 43.7% of newborns in Iran, 60% of newborns in Mexico, and 75% of newborns in Spain being affected [1, 11, 14].

Neonatal Acne

Neonatal acne is characterized by the appearance of open or closed comedones, associated or not with papules and pustules that may occur from the first weeks until the third month of life (Fig. 33.2). It is more frequent on the cheeks, mentum, nose, and scalp [6]. Lesions result from the stimulation of sebaceous glands by maternal

Fig. 33.2 Neonatal acne

and newborn androgens. It may either recede or progress to infant acne [6, 12, 13].

Neonatal Cephalic Pustulosis

Neonatal cephalic pustulosis is a cutaneous eruption comprising inflammatory papules and pustules affecting the face and scalp of newborns in the first weeks of life (Fig. 33.3). Characteristically there are no comedones. Some authors consider it a manifestation of a primary infection caused by *Malassezia sympodialis* [3, 15, 16]. Others suggest that *Malassezia* spp. may be involved in the etiopathogenesis of neonatal acne and neonatal cephalic pustulosis [6, 13]. The lesions disappear spontaneously after 4 weeks of life.

Toxic Erythema

Toxic erythema is a benign and self-limited condition that appears in the first days of life [6]. Its clinical manifestation is a maculopapular eruption comprising white or yellowish papules, 1–3 mm in diameter, on the erythematous macula (Fig. 33.4). The lesions occur most frequently on the anterior and posterior areas of the upper body, but may also frequently affect the proximal regions of limbs (arms and thighs) and face. The lesions evolve to outbreaks of new lesions during a period of 5–7 days, without hypochromia or scars [6, 8, 12]. It does not require any specific treatment. The etiology is unknown; however,

Fig. 33.3 Neonatal cephalic pustulosis

Fig. 33.4 Toxic erythema

several hypotheses have been proposed, such as hypersensitivity to allergens, transient reactions of the skin to thermal or mechanical stimulation of skin, and graft-versus-host reaction induced by maternal lymphocytes transferred before or during delivery. However, the most recent hypothesis indicates a possible inflammatory response to bacteria that penetrate the pilosebaceous follicle [17]. The diagnosis can be done through Tzanck examination with Giemsa staining, in

which numerous eosinophils can be identified. Peripheral eosinophilia may be found in 15–18% of cases. Skin biopsy is not required to confirm the diagnosis, and characteristic findings are subcorneal pustules rich in eosinophils [13]. According to the study by Kanada et al. [14], the incidence of toxic erythema in the United States was 7%. In other countries, incidence varies: 12% in Mexico, 23% in India, 43.6% in China, and 45% in Australia [9, 14, 18]. The frequency in preterm infants is lower than in full-term infants [14]. In another study, the prevalence was greater in term infants, those born through vaginal delivery, those from first gestation, and those fed with formula [18]. Another study found a greater incidence in newborns with greater gestational age and weight at birth [9]. There is a lower incidence in preterm newborns, possibly due to lower inflammatory and immune response. Whether toxic erythema is specific to an ethnic group is not yet known [12].

Transient Neonatal Pustular Melanosis (TNPM)

TNPM is characterized by the appearance of sterile pustules or vesicles without erythematous halo, which are distributed in any part of the body; however, they occur more frequently on the chin, neck, upper chest, and lower chest. Lesions vary up to 0.3 cm in diameter and burst easily (Fig. 33.5). After rupture, they leave a collarette of white scale and residual hyperchromic macula that may vary from 0.5 to 1 cm in diameter [6, 8]. This dermatosis affects both sexes equally, but is more frequent in newborns with African ancestry. Cultures are negative. Histopathologic examination of pustules indicates subcorneal and intraepidermal pustules with content rich in neutrophils and, rarely, eosinophils. The lesions may be present at birth or in the first weeks of life, or even occur inside the uterus. Macules recede spontaneously until 3 months [12]. The frequency of TNPM in newborns was reported as 0.2% in Caucasians, 0.9% in Iranians, and 4.4% in Africans [11, 12].

Fig. 33.5 Transient neonatal pustular melanosis

Infantile Acropustulosis

Infantile acropustulosis is characterized by the presence of recurring outbreaks of pruriginous vesiculopustular lesions with acral distribution (Fig. 33.6), affecting the hands (with predominance of palms) and feet (with predominance of soles) [3]. It mainly affects children with African ancestry and boys [3, 13]. The lesions last from 5 to 10 days, and outbreaks occur again at intervals of 2–4 weeks. The lesions may be present at birth, but normally develop in the first weeks or months of life and may continue until 3 years old [3]. The lesions are usually very pruriginous [6, 13]. The etiology is still unknown, and some authors suggest that it may be due to a reaction pattern in individuals predisposed to infection or infestation. A history of scabies before the diagnosis of infantile acropustulosis is frequent. Results from laboratory studies are generally normal, but cases of peripheral eosinophilia have been reported. Tzanck test or Gram

Fig. 33.6 Infantile acropustulosis

staining of the pustule content usually reveals numerous neutrophils, some eosinophils, and absence of bacteria. Skin biopsy shows intraepidermal or subcorneal pustules with neutrophils and eosinophils. Scabies is the most important differential diagnosis because infantile acropustulosis usually occurs after scabies. In addition, scabies in infants usually progresses with pustules on the soles, and the soles are very similar to those observed in cases of infantile acropustulosis [3, 6]. Other differential diagnoses include toxic erythema and TNPM, both asymptomatic and transient.

Birthmarks

One of the most prevalent vascular birthmarks is the salmon patch, and one of the most prevalent pigmentary birthmarks is Mongolian spot. The frequency of these marks varies among ethnic groups, with the former being more frequent in Caucasians and the latter more frequent in Asians, Native Americans, and black-skinned persons [9, 14]. Hemangioma and capillary vascular malformation as well as congenital melanocytic nevus and café-au-lait spots are other examples of vascular birthmarks and pigmentary birthmarks, respectively, and are frequently found in newborns (see later discussion).

Fig. 33.7 Salmon patch

Salmon Patch or Nevus Simplex

Salmon patch on the nape is popularly known as "stork's bite," whereas that on the glabella is known as "angel's kiss." These are vascular patches of reddish or rose color (salmon) located on the occipital and nape regions, glabella, forehead, upper eyelids, and nasolabial regions that disappear when pressed with a finger (Fig. 33.7). It is distributed mostly on the occipital region (10.6–37%), glabella (20%), and eyelids (15–90.8%) [8, 9, 19]. Overall, lesions become more

evident when the child cries or after a bath. Histologically the lesions comprise ectatic dermal capillaries. The lesions on the eyelids tend to disappear after the third month of life. Glabellar lesion, in general, disappears after the first year of life. Occipital patch may persist in 50% of adults. In the United States, Kanada et al. [14] observed that the most common lesion was the salmon patch, affecting up to 83% of newborns and being more frequent in Caucasians and less frequent in African Americans. Moreover, they observed that the salmon patch was less frequent in preterm infants. Other studies showed that the incidence of the salmon patch varied from 1.7% to 55.5% in different countries [11, 14, 19].

Mongolian Spots

This dermatosis comprises a grayish blue patch, sometimes greenish or bluish, of varied sizes and forms, with diameter varying between 3 and 10 cm (Fig. 33.8). In the majority of cases it is located on the gluteal, sacral, and lumbar regions. In some cases, the patch may be more extensive (ectopic Mongolian spots) and affect the shoulders and upper and lower limbs. It presents racial variation and has a tendency to recede spontaneously. Spontaneous receding is expected in the majority of cases with typical locations [16]. This is enough to distinguish Mongolian spots from other dermal melanocytosis. Histologically, in the area of the spot, dermal melanocytes are found in the deep and middle layers of the dermis. The destruction of the melanocytes begins during fetal life and is maintained in the child's first years of life. In the case of persistent
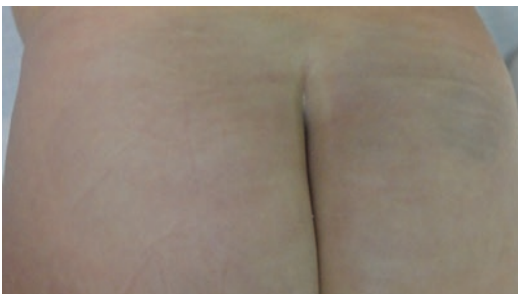
Fig. 33.8 Mongolian spot

Mongolian spots, formation of dermal fibrosis and vascular proliferation near the dermal vessels may occur. Mongolian spots may be due to blockage of migration of melanocytes from the neural crest and thus being retained in the dermis. The greater the intensity of the color in children at 1 year old, the greater size of the patch will be at 2 years of age [8]. Mongolian spots are observed in all ethnic groups, but it is more prevalent in African descendants, Asians (Pacific Ocean coast), and Native Americans. The second most frequent lesion found by Kanada et al. [14] in North America was Mongolian spots (20% of cases), which was more frequent in children with Asian, African American, Native, and Hispanic ancestries [14]. The prevalence described in the different countries was 86% in China, 81% in Japan, 77% in Mexico, 71.3% in Iran, 60.2% in India, and 45% in Brazil [5, 8, 14, 11].

Vascular Lesions

Knowledge of vascular lesions has progressed in the last decades, and since its first publication by Mulliken in 1982, who divided vascular lesions into two major categories (vascular hemangioma and malformations), much information has been gathered. In 1996 this classification was revised, and vascular lesions were divided in tumors and malformations [20]. Hemangioma is a vascular tumor characterized by a proliferative and an involution phase. Malformations are defects in development that cause dilation of the capillary, venous, arterial, or lymphatic vessels [16, 21]. Hemangioma varies in frequency from 0.2% to 4.5% until the third month of life, whereas capillary vascular malformation may be found in 0.3% of newborns [11, 12]. Pigmentary birthmarks are common in newborns, and its frequency may vary among different studies (congenital melanocytic nevus, 0.6–2.4%; café-au-lait spots, 0.4–1.3%) [9, 11, 14].

Hemangioma

Infantile hemangiomas are the most common tumors in childhood (Fig. 33.9). Infantile
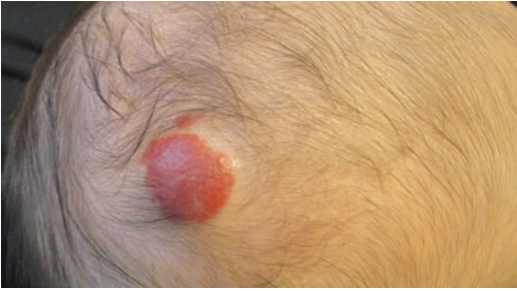
Fig. 33.9 Infantile hemangioma

hemangioma may be present at birth, but generally develops during the first weeks of life as precursor lesions that develop over normal skin. In 90% of cases, hemangiomas are observed during the first month of life [8, 21]. The most frequent precursor lesions are anemia spot, telangiectasia, and macula or patch. Histologically, the proliferative phase comprises clusters of tumoral cells (endothelial) that express *GLUT1* and *CD35* [20]. In infantile hemangioma, the angiomatous lesion has accelerated growth in the first 6–10 months [8, 20]. The natural history of infantile hemangioma is specific and may be divided into six phases: nascent, early proliferative, late proliferative, plateau, involution, and abortive [20]. The prevalence of infantile hemangioma in Caucasian newborns has varied among studies, from 3% to 12% [21–23]. Anderson et al. [21] found that the incidence of hemangioma in Olmsted County (Minnesota, USA) increased in the last three decades from 1.64 per 100 person-years to 1.97 per 100 person-years. A study in Iran has shown that infantile hemangioma was present in 1.3% of 1000 newborns [11]. Most cases of infantile hemangioma are self-limited and recede partially or totally up until 5 years of age. Nevertheless, some hemangiomas may result in significant complications such as disfigurement, transient or permanent functional alterations, and pain (in the presence of ulceration). Several studies indicated patient-related factors involved with hemangioma such as female sex, Caucasian, low birth weight, and erythropoietin therapy. Maternal factors may also increase the risk, such as mother's advanced age, antenatal vaginal bleeding, pre-eclampsia, amniocentesis, multiple gestation, and in vitro fertilization

[11, 21–23]. Haggstrom et al. [22] found in their study that a family history of hemangioma did not significantly differ between infants with hemangiomas and the general population.

Capillary Vascular Malformation

Vascular malformations are alterations in the vascular development present at birth and do not present a tendency for involution. Frequently, these vascular patches have unilateral segmental presentation and respect the midline [8]. The capillary vascular malformations are also called port-wine stains or nevus flammeus (Fig. 33.10). Histologically they are characterized by capillary vessels or ectatic superficial dermal venules and absent vascular proliferation [8, 24]. The growth of these lesions occurs throughout the child's growth, and the most common areas are the face, neck, and limbs. During infancy the color varies from rose to erythematous, and during adulthood

Fig. 33.10 Port-wine stain

it becomes wine colored, with the macular component being replaced by nodular surface plaques. They occur in approximately 0.3–1.2% of the population [8, 14, 19, 24].

Congenital Melanocytic Nevus

Congenital melanocytic nevus is a benign melanocytic proliferation that may be present at birth or appear before the first years of life. The majority of melanocytic nevi grow proportionally with the child's growth. Depending on the size they reach during adulthood, they may be small (<1.5 cm), medium (1.5–19.9 cm), and giant (≥20 cm) (Fig. 33.11). There are no significant differences regarding frequency among sexes [25–27]. The estimated frequency of giant congenital melanocytic nevus is 1:20,000 [26]. Meanwhile, the reported frequency of small melanocytic nevus varied among studies, with 0.6% in Taiwan, 1–2.4% in the United States, 2% in India, 2.1% in Australia, and 2.46% in Brazil [1, 2, 5, 10, 19, 27]. The variation found in these studies may be explained by the different follow-up durations of newborns (late congenital melanocytic nevus may not be detected

in a short-duration follow-up), examination performed by a nondermatologist doctor, and diagnostic method (clinical versus histologic) [25]. In addition, there are variations in the prevalence of congenital melanocytic nevus among different ethnic groups (fair versus dark skin). Some studies showed that newborns of non-European origin have approximately twice more congenital melanocytic nevus than Caucasian newborns of European origin (2.2–5.3% in European newborns versus 7–12.5% in non-European newborns) [25]. Furthermore, at the end of the first decade of life, melanocytic nevi range from 15 to 30 lesions in Caucasian children and between 5 and 10 lesions in children from other ethnic groups (Africans, Native Americans, and Asians) [28].

Café-au-Lait Spots

These macules are patches of light coffee color, similar to the drink café-au-lait. The lesions present uniform tonality and well-defined limits, with sizes varying from few millimeters to centimeters (50 cm) in diameter (Fig. 33.12). The lesions may be present at birth or appear afterward. Studies have shown that single café-au-lait spots are common and have a frequency from 2.5% to 25% in healthy children from different ethnic groups. The frequency of café-au-lait spots varies among different ethnic groups and differs when the study is conducted with newborns or children at school. The frequency in newborns was 0.4% in Taiwan, 0.4% in China, 1.3% in

Fig. 33.11 Giant congenital melanocytic nevus

Fig. 33.12 Café-au-lait spots

India, 0.04% in Finland, 1.7% in Finland, 0.3% in Iran, and 3.45% in Brazil [9, 10, 11, 14, 19, 29–31]. In the United States, a study showed the presence of at least one café-au-lait spot in 2% of Caucasian newborns, 2% in Hispanic, and 7% in African Americans [14]. Studies have evaluated the frequency of more than one café-au-lait spot in healthy children, reporting that two or more café-au-lait spots were present in 0.7–6.9% of children and three spots in 0.2–0.3% of healthy children [32, 33]. Multiple café-au-lait spots may be present in various genodermatoses. Neurofibromatosis type 1 (NF1) is the main genodermatosis associated with café-au-lait spots, and these spots usually increase in number and size in the first decade of life. The diagnostic criteria for NF1 were established in 1988 by the National Institutes of Health Consensus Conference and were revised in 1997 [34]:

1. Six or more spots >0.5 cm in diameter in children younger than 5 years or six or more spots greater than 1.5 cm in diameter in children older than 5 years
2. Two or more neurofibromas of any type or one plexiform neurofibroma
3. Axillary ephelides
4. Optic glioma
5. Two or more Lisch nodules
6. Characteristic bone lesions, including sphenoid dysplasia or thinning of long bone cortex with or without pseudarthrosis
7. First-degree relative with confirmed diagnosis of NF1

The presence of two or more criteria enumerated above is required for the clinical diagnosis of NF1

Glossary

Comedo A clogged hair follicle resulting in infundibular dilation and thinning of the follicular wall. It possesses a plug composed of loosely arranged keratinized cells and sebum.

Erythema Redness of the skin, caused by increased blood flow in superficial capillaries. It occurs with any skin injury, infection, or inflammation. Erythema disappears on finger pressure (blanching), while purpura or bleeding in the skin and pigmentation do not.

Melanosis Abnormally dark pigmentation of the skin or other tissues, resulting from a disorder of pigment metabolism.

Pustulosis A highly inflammatory skin condition resulting in large fluid-filled blister-like areas, or pustules. Many neutrophils are present within the cavity of a pustule. The epidermis surrounding the pustule shows slight acanthosis, and an inflammatory infiltrate can be seen beneath the pustule.

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Cutaneous Aging and Dermatosis in Geriatric Patients

34

Leticia Maria Eidt

Key Points
- Aging is a dynamic and progressive process in which there are morphologic, functional, biochemical, and psychological changes that determine loss of the individual's ability to adapt to the environment, causing greater vulnerability and higher incidence of pathologic processes
- The skin undergoes the processes of intrinsic and extrinsic aging, each of which presents different clinical and histologic features
- Intrinsic or chronological skin aging is related to physiologic metabolic changes, affects all persons, and is inevitable. It is usually found in sun-protected areas and is attributed to intrinsic factors, for example, genetic predisposition and changes in the endocrine environment, and reflects degradation processes of the entire organism
- Extrinsic skin aging is also referred to as photoaging as it is caused mainly by ultraviolet radiation. Besides the ultra-violet radiation, infrared radiation and tobacco smoking are by far the most aggressive environmental agents
- There is no exclusive dermatosis of the elderly, although some dermatoses are more prevalent in the older population

Epidemiology

Aging of the Population

The world population of older adults is increasing significantly. This global transformation characterized by the aging of the population is known as demographic transition [1]. Over the past few years, the world's population has continued on its remarkable transition from a state of high birth and death rates to one characterized by low birth and death rates. The control over infectious disease contributes to this aging population. Other factors also contribute: improved life conditions and alimentary habits, physical exercise, immunization measures, periodic medical examinations, and the use of medicines with proven effectiveness against many diseases [2]. At the heart of this transition has been the growth in the number and proportion of older persons [3].

The population of elderly people, traditionally defined in developed countries as those

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aged >65 years, is constantly growing [4, 5]. In developing countries the elderly are defined as those aged >60 years [2, 5]. According to the World Health Organization (WHO) predictions, the global population aged >60 years will reach 2 billion in 2050. In general, the female outlives the male among humans and most other species [6]. In most countries, women live on average 7 years longer than men [1].

The older population itself is aging. By the year 2050, one-fifth of the global population will be older than 65. Of interest is the fact that those 85 years and older make up the fastest growing segment of the population. The increase in the number of very old people (≥80 years) is projected to grow by a factor of from 8 to 10 times on the global scale between 1950 and 2050 [3].

As aging in developing countries is more rapid than in developed countries, developing countries will have less time than the developed ones to adapt to the consequences of population aging. There are implications of an aging society for a whole range of social institutions, for health services, for education of society and families of the old people. An increasing number of persons is expected to require specialized services such as health, recreation, housing, and nutrition [3].

Several conditions occur as a consequence of advancing years of life. These include the major fatal diseases such as cardiovascular diseases, cancer, brains injuries such as strokes, metabolic disorders such as type 2 diabetes mellitus, osteoporosis, and dementias such as Alzheimer's disease [3]. A basic understanding of the aging process will enable healthcare providers to distinguish age-related physiologic changes from disease-related pathologic processes [3].

The greatest challenge for humanity is not only the speed at which the population is aging, but the related quality of life. According to Nascimento [2], aging with dignity and improved quality of life have become the rights of senior citizens and duties for the society to which they belong.

> **Box 34.1 Important Note**
> The size of the world's elderly population has been growing for centuries. What is new is its rapid increase. One in every ten persons is now ≥60 years old. By 2050, one in five will be ≥60 years old and by 2150 one in three persons will be ≥60 years. Population aging is a natural phenomenon, irreversible and worldwide.

Concepts and Etiopathogenesis

Aging and the Geriatric Patient

Aging is regarded as a dynamic and progressive process whereby morphologic, functional, biochemical, and psychological changes determine loss of the individual's ability to adapt to the environment, causing greater vulnerability and higher incidence of pathologic processes that may induce death. This means that aging is characterized by reduction of homeostatic functional capacity in situations of corporeal overload [7].

Aging can be understood as a natural process of a gradual reduction in the functional reserve of individuals, known as senescence, which under normal conditions does not usually cause problems. However, overload conditions such as illness, accidents, and emotional stress can cause a pathologic condition (senility) requiring intervention and assistance. Sometimes it is quite difficult to differentiate between normal aging and disease [8].

According to Peryassú [9] and Freitas and Machado [10], various theories are seen as responsible for the aging of organisms. These are divided into two main groups: Stochastic Theory and Systemic Theory. Somatic mutations, catastrophic error, oxidative damage and free radicals, the wear and tear of altered proteins, dedifferentiation, accumulation of waste, and post-translational protein represent the group under the Stochastic Theory, or occurrence by chance. Genetics, neuroendocrine, immune, and metabolic conditions belong to the group under the Systemic Theory.

The elderly, defined as those persons aged >60 years in developing countries [2, 5] and >65 years in developed countries [4, 5], needs holistic attention. This involves the handling of the physical, mental, functional, and social aspects of acute and chronic diseases, their prevention and rehabilitation, and palliative care of the elderly [5]. To take care of this special group, an interdisciplinary team with the objective of optimizing functional capacity and improving quality of life and the autonomy of the elderly is necessary. And, of course, a dermatologist is a necessary member of this team [3].

The practice of providing daily assistance to geriatric patients involves the following: heterogeneity of patients and scenarios of care, functional changes in the elderly, concomitance of multiple diseases (plurimorbidity) including geriatric syndromes ("the giants of geriatrics"), difficulty identifying all the problems (iceberg phenomenon), polypharmacy, fragility, vulnerability, the various losses that the elderly show, and terminality [5].

Functional changes in the elderly Around 60 years of age, depending on the person, it is necessary to take more care with the body because its physical condition becomes gradually different from those presented at previous ages. Several changes occur in the organs and systems of the human body during the natural aging process [11].

An easy change to detect is body weight, which remains unchanged or decreases as a result of decreased organ weights, the replacement of functional tissue by adipose tissue (which is lighter), and a decrease in the number of cells of which they are composed. It is also observed that the height of individuals reduces by approximately 1 cm every 10 years [11].

The thickness, resistance, and bone architecture of the skeleton also gradually decrease. These changes can be modulated by dietary habits, physical activity, and hormonal factors, especially in women after menopause. The same can be inferred with respect to muscles, in which the number and diameter of the muscle fibers decrease [11].

Different changes are observed in the respiratory system of the elderly: decreased lung elasticity, decreased chest wall compliance, reduced cleaning ability of the airways, and increased volume of air in the peripheral bronchi. They are also predisposed to respiratory infections [11].

Gradual changes occur in organs that make up the digestive system: decreased food processing capacity during digestion, mainly by decreasing the activity of digestive enzymes. Decreased peristalsis, reduced liver volume, and decreased hepatocytes and hepatic enzyme activity also occur, in addition to a decline in production of bile. Many drugs are metabolized in the liver, and the elderly have different metabolic activities compared with younger people. Therefore, lower doses of certain drugs may be necessary [11].

The urinary system undergoes multiple changes in its function as a person ages. The number of nephrons decreases, leading to decreased functional ability of the kidneys and decreased sodium metabolism. As the elderly often use medications, change in kidney function may lead to a lower elimination of these substances, with a consequent increase in the current concentration and increased side effects of pharmacologic agents. Urinary incontinence situations occur more frequently in the elderly but are not part of normal aging [11].

The cardiovascular system is strongly influenced by environmental conditions and lifestyle. Therefore, some changes are physiologic and due to the aging process, whereas others are influenced by lifestyle, including physical activity and nutrition. In general, the elderly are observed to have decreased cardiac output, increased maximum heart rate, decreased stroke volume, increased resistance to ejection, decreased cardiac complacency, irregularities in automaticity, and decreased elasticity of the arteries [11].

The blood itself undergoes no obvious changes with the aging process. However, changes resulting from other systems and tissues can influence the cellular and plasmatic composition of blood. For example, with a decline in hematopoietic capacity, the formation of fewer erythrocytes can cause anemia in the elderly. Changes in the type

and amount of circulating leukocytes result from aging of the immune system [11].

Aging of the immune system is accompanied by a decrease in T and B lymphocytes and loss of phagocytic capacity. These changes are associated with increased incidence of infections, autoimmune diseases, and cancer, all of which greatly contribute to morbidity and mortality in the elderly population [11].

With regard to the reproductive system, there are important differences in the aging process of women and men. Women go through the menopause, when there are significant hormonal changes, loss of reproductive capacity, and changes in reproductive organs and other systems. In women, these hormonal changes may be risk factors for the development of diseases that lead to loss of quality of life in elderly women. In men there is a very gradual decline in reproductive capacity [11].

Among the effects of aging on the endocrine system, changes were observed in the levels of production and hormone secretion, transport and metabolism of hormones, the regulation of hormone release, and the responsiveness of tissues to hormones [11].

With aging of the nervous system there is a decrease in conduction and response speed, which makes the reaction to a stimulus slower. Another aspect of nervous system aging is the changes that occur in the organs of the senses: decreased skin sensibility and decreased taste sensitivity; change in the perception of frequencies and auditory tones, tending to deafness; decreased perception of light due to change in the cellular structure of the eye and lens opacity; loss of olfactory ability; and decreased skin sensitivity [11].

Multiple diseases/plurimorbidities The description made previously of the possible functional changes that occur during aging leads to understanding of the fact that the elderly are more susceptible to the prevalence of various diseases.

The illnesses that affect the elderly are cardiovascular, respiratory, cerebrovascular, and the musculoskeletal disorders, cancers, and many other chronic diseases [12]. These include peripheral arterial disease [13], esophageal cancer [14], chronic bronchitis and pulmonary emphysema [15], prostate cancer [16], labyrinthitis [17], urinary tract infections [18], skin cancer [19], angina pectoris and acute myocardial infarction [20], stroke [21], lung cancer [22], stomach cancer [23], respiratory infections [24], dyslipidemias [25], oral cancer [26], malnutrition [27], diseases of thyroid [28], sedentary lifestyle [29], diabetes mellitus [30], osteoporosis [31], cervical cancer [32], disease of the oral cavity [33], urinary incontinence [34], adverse drug reactions [35], pressure ulcers [36], AIDS [37], dementias [38], depression [39], breast cancer [40], obesity [41], colon and rectal cancer [42], and hypertension [43], among others [6].

Geriatric syndromes Elderly health is determined by the harmonic functioning of four functional domains: cognition, mood, mobility, and communication. The loss of these functions results in the major geriatric syndromes addressed: cognitive impairment, postural instability, immobility, sphincter incontinence, and communicative disability [44].

The evolution of loss of cognition, mood, mobility, and communication function results in clinical syndromes that can be found in the elderly: cognitive impairment (delirium, dementia, depression, mental illness), postural instability (balance and risk of falls), immobility (risk of pressure ulcers), sphincter incontinence (urinary and fecal), constipation and fecal impaction, polypharmacy (resulting in iatrogenic conditions), osteoporosis, malnutrition, sleep disorders, family and social isolation, sexual dysfunction, dysphagia, sensory loss (vision, hearing), difficulty of communication, and communicative disability.

Iceberg phenomenon Diseases known to the physician represent only the tip of the iceberg [45]. Sometimes there is difficulty in identifying all the problems and discovering undiagnosed pathologies in elderly people. Although cardiac, respiratory, and neurological disorders have been known to a patient's personal physician, dementia, anemia, incontinence, and immobility only rarely have been recognized [46].

Polypharmacy The medical literature has shown that aging predisposes to an increased consumption

of prescription or over-the-counter drugs. However, it is known that physiologic changes related to aging, such as the modification of body composition and reduction in hepatic and renal functions, tend to significantly alter the pharmacokinetics and pharmacodynamics of various drugs, which increases the elderly's susceptibility to adverse [47] or more intense therapeutic effects [48]. Such polypharmacy predisposes iatrogenesis.

The literature has suggested different concepts for the term polypharmacy. Some authors consider polypharmacy the use of five or more drugs [49] while others consider the use of at least one non-prescription medication in a list of supposedly necessary prescriptions [50].

Scenarios of care The conquest of longevity shows the elderly in its many dimensions and requires different approaches and attention to the situation of being elderly [51].

Issues related to elderly care are complex and of great importance. Understanding the elderly as one singular person, in a family and social context, should be one of the principles that guide their care. Some specific aspects need to be considered: a global assessment focusing on functional, psychological, social, and environmental aspects needs attention. Patients' autonomy and independence should be evaluated and respected. Knowledge of the patient's residence and knowing whether the patient is alone, with family, or in a long-term care facility for seniors also interacts with the planning of care for the geriatric patient [52].

In summary, the geriatric patient needs to be more closely monitored because of increased fragility of the skin, the physical limitations that hinder compliance with prescribed regimens of treatment, the presence of numerous comorbidities, polypharmacy, and the physiologic and functional changes that take place in the elderly.

Cutaneous Aging

Cutaneous aging, a highly complex but not yet fully understood process, is particularly interesting because of the continuously increasing life expectancy in many countries [53].

Like all organs, skin suffers progressive decrement with increasing age [54]. Aging results in numerous adverse changes in the structure and function of multiple human organs, including the skin. Thus, the elderly population will pose significant challenges not only to physicians in geriatrics but also to those in other specialties, including dermatology [4].

As a consequence of the increase in life expectancy, various organs of the human body, including the skin, age. Thus, the aging population is a challenge also faced by dermatologists because the demographic transition increases the possibility of skin diseases that need to be treated.

One of the perceived aspects of aging is the cluster of changes in skin and its annexes (hair, hair and nails) as a person ages. This is due to the fact that for humans, sight is the sense that we most use to identify the environment around us, and we therefore direct more attention to what we see. As the skin is the organ that externally covers our body, skin changes are the most visible and are used as a criterion to indicate that someone is growing old.

Skin aging is thus particularly important because it affects human health, produces social impact because of its visibility, and is an ideal model to research aging, given its accessibility and well-demonstrated interactions between cell precursors and differentiated cells and between cells and the dermal matrix [55].

Some researchers [56, 57] found that skin aging can occur in senescent form (physiologic) or senile (pathologic). In senescence, organic, functional, and psychological changes are themselves of advancing age, whereby various organs and systems may change without compromising the balance and homeostasis. In senility the changes result in an imbalance, leading to the possibility of disease. Sometimes it is difficult to establish the line between physiologic and pathologic changes.

Several theories have been developed to comprehend the progressive process of skin aging. Aging may be considered as the accumulation of different deleterious changes in cells and tissues. These changes may progressively impair biological functions, increase the risk of developing disease, and ultimately lead to death [53].

The skin undergoes the processes of intrinsic and extrinsic aging [4], each of which presents different clinical and histologic features [4, 53]. Intrinsic or chronological skin aging is related to physiologic metabolic changes, affects all persons, and is inevitable. It is usually found in sun-protected areas [53] or in non-exposed areas and is attributed to intrinsic factors, for example, genetic predisposition and changes in the endocrine environment, and reflects degradation processes of the entire organism [54]. It is characterized by the thinning of the upper cutaneous layers, a decrease in the amount of lipids, diminished blood flow, and fragmentation of collagen. This leads to dry, pale skin with fine wrinkles [4, 53].

Extrinsic skin aging is also referred to as photoaging as it is caused mainly by ultraviolet radiation [4]. It is also known as actinosenescence or dermatoactinosenescence [58]. However, various environmental, physical, chemical, and mechanical insults can collaborate in the process. Besides ultraviolet radiation [59], infrared radiation and tobacco smoking are by far the most aggressive environmental agents [54], leading to the accumulation of abnormal elastin and the disintegration of collagen fibrils [4]. Exposed areas of the body such as the face, neck, and hands are the most affected areas, and overexposure of these regions may result in premature skin aging [54]. Clinical manifestations include deep wrinkles, skin laxity, hyperpigmentation, senile lentigines, and a leathery appearance. In the most severe cases skin remodeling leads to dermatoporosis, which represents chronic cutaneous failure and fragility syndrome [4].

The skin altered by intrinsic aging is usually lighter, delicate, looks fragile, and has fine wrinkles and loss of elasticity features. Already photodamaged skin, resulting from the overlap of extrinsic factors with chronological aging, features rough appearance, with deeper wrinkles and irregular pigmentation, tending to hyperchromia [60].

The proper histopathologic aspects of skin aging are noticeable in the three skin layers: epidermis, dermis, and hypodermis [8, 54, 59, 61–63]. The epidermis decreases in thickness by reduction in the volume of the cells, decrease in the number and activity of melanocytes, and reduction of Langerhans cells responsible for the defense of the skin. At the dermal-epidermal junction a flatness of the epidermal papillae and interpapillary cones is observed, leading to a similar development.

In the dermis major changes occur: the number of fibroblasts decreases, collagen fibers become more rigid, elastic fibers show changes of the elastin, the number of mast cells decreases, there is atrophy of sweat glands, sebaceous glands are reduced in function, and the sensory organs decrease in number and volume. In the hypodermis there is a decrease of the number and size of fat cells.

In cutaneous aging various changes in the skin are observed: skin atrophy and diffuse thinning, yellowish and grayish tone, loss of elasticity and turgor, decreased sebum and sweat secretion, diffuse decreased pigmentation, reduction of defense and immunity cells, bleaching and reduction of the number of hair and nail changes [54, 57, 61, 62, 64–67].

Aging of the skin is commonly associated with increased wrinkling, sagging, and laxity, but when considering the underlying reasons for these changes it is important to distinguish between the effects of true biological aging and environmental factors, such as exposure to the sun [60].

Intrinsic or chronological skin aging The process of intrinsic skin aging is similar to that occurring in most internal organs, involving slow deterioration in tissue function. It is largely genetically determined and clinically associated with increased fragility and loss of elasticity, and appears transparent.

The stratum corneum remains relatively unchanged, but the epidermis and dermis thins with a flattening of the dermoepidermal junction. There is also reduction in the number and biosynthetic capacity of fibroblasts and progressive disappearance of elastic tissue in the papillary dermis. Skin collagen content decreases with age and the fine collagen fibers associated with infancy become increasingly dense and tightly packed, and far more randomly orientated.

The processes associated with intrinsic skin aging are thought to result from a combination of different events: decreased proliferative capacity of skin-derived cells such as keratinocytes, fibroblasts, and melanocytes; decreased matrix synthesis in the dermis; and increased expression of enzymes (metalloproteases) that degrade the collagenous matrix. Cellular senescence involves the arrest of cellular growth at G_1 phase when cells reach the end of their replicative life span. The senescent cells cannot be stimulated to enter S_1 phase by physiologic mitogens. An alternative aging hypothesis is the oxidative stress theory, which cites the possibility of free radicals causing damage to the connective tissue components of the dermis, particularly collagen [60, 68].

Extrinsic skin aging Extrinsic aging primarily results from exposure to ultraviolet light. It has been suggested that as much as 80% of facial aging is attributable to sun exposure. Clinically, photodamaged skin is characterized by loss of elasticity, increased roughness and dryness, irregular pigmentation, deep lines and wrinkles, and premalignant and malignant lesions [59, 69].

Changes that occur in the epidermis of photodamaged skin, including both increase and decrease of epidermal thickness (corresponding to hyperplasia or severe atrophy, respectively) and loss of epidermal polarity, and changes in the proportion and/or functionality of the dermal extracellular components account for the major visible changes associated with ultraviolet-induced extrinsic damage [60, 68].

Changes are seen in all three components of connective tissue: collagen fibers, elastic fiber network, and glycosaminoglycans. These changes lead to a massive accumulation of so-called elastotic material in the upper and mid dermis. The process by which this elastotic material is first formed is still unclear, but likely involves degradation of existing elastic fibers and dysregulation of elastin and fibrillin production [60, 68] (Fig. 34.1).

The metalloproteinases (MMPs) are degradative enzymes responsible for matrix degradation in skin. The combined action of MMP1, MMP2, and MMP9 can fully degrade skin collagen and components of the elastic network. The basal

Fig. 34.1 Deep wrinkles (nuchae rhomboidalis)

expression of these enzymes in "normal" skin is relatively low. However, they can be markedly upregulated by ultraviolet radiation, causing massive elastosis and collagen decrease [70] and degeneration of collagen [60, 68].

Other factors besides ultraviolet exposure can contribute to extrinsic aging. A study on the influence of environmental factors of facial aging [71] showed that 40% of the variation in perceived age is due to non-genetic factors and that there is a negative influence of sun exposure, as well as smoking and low body mass index, on facial aging. Freiman et al. [72] and Kennedy et al. [73] showed that smoking is strongly associated with premature skin aging. Other studies also demonstrated a relationship between smoking and photodamage [67, 74, 75].

The changes observed in the intrinsic and extrinsic skin aging process, from both the molecular and histopathologic point of view, are responsible for the clinical consequences of cutaneous manifestations in the elderly. The skin changes can range from simple wrinkles to premalignant and malignant lesions [68].

Dermatosis in Geriatric Patients

As the geriatric population continues to grow, more aged patients are being admitted to dermatology services. The successful management of these patients requires the understanding of the features of geriatric patients and prevalence of skin diseases in this group.

Aging skin undergoes progressive degenerative change. The structural and physiologic changes that occur as a natural consequence of intrinsic aging combined with the effects of cumulative extrinsic damage and environment insult can produce a marked susceptibility to dermatologic disorders in the elderly. However, it is important to note that there is no exclusive dermatosis of the elderly, although some dermatoses are more prevalent in this population.

Some considerations about the diagnoses and the management of cutaneous disorders in the elderly are noteworthy. In all elderly patients, total dermatologic examination must be performed because it may reveal some severe cutaneous or underlying noncutaneous diseases detected incidentally at examination [76]. The prevalence of polypharmacy in this population increases the risk for autoimmune drug reactions, and diagnosis should be undertaken with an awareness that polypharmacy creates a greatly increased susceptibility to drug eruptions in the elderly that can mimic other cutaneous disorders. Thus the prevalence of polypharmacy can profoundly complicate accurate diagnosis of dermatologic disorders [77].

It is not uncommon for older patients to have multiple impairments, with the potential for cognitive dysfunction as well as impaired vision, hearing, or mobility. In addition, they may not have adequate housing or nutrition, or the financial resources necessary for adequate compliance. Physicians must take into consideration the patient's physical ability to comply with the recommended therapy as well as socioeconomic factors that may affect compliance [77]. Consequently, in the management of elderly patients a social and physical evaluation should be carried out and treatment must be recommended accordingly [76].

Management of dermatologic disorders in the elderly is often less than optimal, owing to the fact that the special needs and limitations of this population are not adequately considered. Treatments should consider the intrinsic differences between younger and older patients that may have an impact on diagnosis and therapy choice. The aged patient is often afflicted with numerous comorbidities that can influence the choice of therapy [77]. For example: simple topical regimens are preferable to systemic drugs.

Different studies [2, 54, 56, 61, 64, 65, 78–80] have reported the prevalence of dermatosis in the elderly population. It is important to know the most prevalent skin diseases in the elderly to determine the appropriate time to initiate prevention measures and establish the optimal treatment.

A study in of 209 patients in Turkey [76] emphasized the importance of full skin examination in the elderly for the detection of cutaneous and noncutaneous diseases unknown to patients. The most commonly diagnosed skin diseases were chronic eczema and those on photodamaged skin. Some severe systemic diseases were also diagnosed.

Another study also conducted in Turkey [81] with 4,099 geriatric patients demonstrated that the five most prevalent dermatoses were eczema, fungal infections, pruritus, and bacterial and viral infections. Moreover, in women, rheumatologic and mucous membrane disorders were the most prevalent, whereas in men the most prevalent were fungal, bacterial, and viral infections, disorders in the legs, ulcers, and vesicobullous diseases.

A study of 100 geriatric patients conducted in New Mexico [82] showed that the most prevalent dermatoses were solar lentigo, seborrheic keratosis, Favre-Racouchot disease, nevus ruby, and guttate hypomelanosis. Actinic keratosis, onychodystrophy, and xerosis was also diagnosed.

In Ohio (USA), Farage et al. [77] reported the presence of vascular diseases (stasis dermatitis and pressure ulcers), autoimmune diseases, adverse drug reactions, infectious diseases (herpes zoster), xerosis, and eczema.

In India [83] a survey conducted in 200 patients aged 65 years or older showed various dermatologic manifestations. Wrinkles, generalized itching, psoriasis, fungal infections, viral infections, pyoderma, leprosy, macular amyloidosis, papular dermatosis nigricans, androgenetic alopecia, onychodystrophy, and onychomycosis were reported by these authors.

Research among 1,518 elderlies in Tunisia [84] demonstrated that fungal infections were the most common, followed by benign tumors, eczema, keratinization abnormalities, bacterial and viral infections, and pruritus.

Brazilian data about the prevalence of skin diseases in the elderly are scarce. A study of 75

elderly residents in a long-stay institution for the elderly in the city of Santos, SP [56] reported that the main skin diseases found were melanosis, seborrheic keratosis, onychomycosis, nevus ruby, senile purpura, xerosis, scabies, and malignancy .

In a study of 210 patients >80 years old in São Paulo [85], the most frequent dermatoses were actinic keratosis, malignant tumors, keratosis seborrheic, onychomycosis, pruritus, xerosis, epidermal cysts, seborrheic dermatitis, drug eruptions, melanosis, and contact dermatitis.

Campbell and colleagues [79] evaluated three groups of elderly: hospitalized patients, ambulatory patients who visited the Dermatology clinic, and healthy volunteers. The most frequent findings were wrinkles, absence of lunula, longitudinal grooves on the nails, cherry angioma, xerosis, actinic keratosis, guttate hypomelanosis, fungal infections, and seborrheic dermatitis. Statistically significant differences between the three groups were not detected.

A survey of 150 elderly patients admitted to a geriatric institution in Rio de Janeiro [80] revealed disorders grouped into 11 eleven different categories, namely manifestations of actinosenescence, keratoses, alopecia, hair system disorders, nevi, benign and malignant tumors, flexural dermatoses, eczema and pruritus, infectious dermatoses, and onychopathies.

A multicenter study conducted by the Brazilian Society of Dermatology [78] showed that premalignant and malignant lesions were the main causes of dermatologic consultations in Brazil among people aged 60 years and 65 years or older, respectively in the year 2006.

Eidt [86] studied 312 elderly people in a referral geriatrics service (ambulatory and inpatient) and in a long-term care facility for seniors, and found 128 dermatologic manifestations. Solar melanosis, guttate hypomelanosis, cherry hemangioma, longitudinal striae on the nails, wrinkles, melanocytic nevi, seborrheic keratosis, male androgenetic alopecia, cutaneous xerosis, telangiectasias, absent lunula, interdigital intertrigo of the toes, skin atrophy, and poikiloderma were present in more than 50% of the participants in this study. Actinic keratosis, white hair, hirsutism, rhomboid skin, supraciliary madarosis, onycholysis, purpura, onychodystrophy, stellar scar, ochre dermatitis,
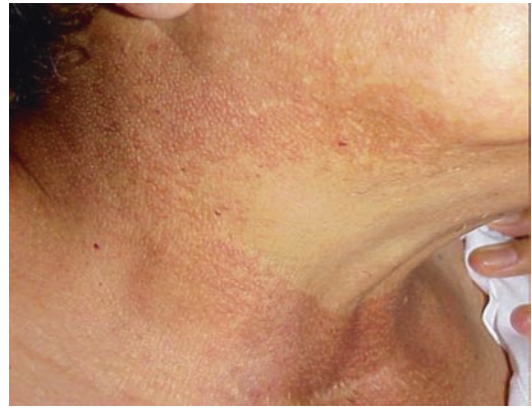
Fig. 34.2 Poikiloderma

acrochordon, dermatosis papulosa nigra, comedo, and keratosis of the elbows and knees were present in 30–50% of the subjects. Dilated pores, female androgenetic alopecia, hypertrichosis of the ears, seborrheic eczema, milia, melasma, different types of scar, plantar calluses, leukonychia, folliculitis, and sebaceous hyperplasia were found in 10–30% of the elderly who participated in the study (Fig. 34.2).

Another consideration concerns the effect of menopause on the skin. Problems encountered by postmenopausal women include atrophy, dryness, pruritus, loss of resilience and pliability, dry hair, alopecia, and easily traumatized skin. The skin of postmenopausal women is thinner and less lubricated than her premenopausal counterparts, increasing the risk for ulceration and infection, including human immunodeficiency virus (HIV) transmission [87].

In addition to the previously presented dermatoses, one should bear in mind skin manifestations of systemic diseases and adverse drug reactions resulting from polypharmacy used by the elderly population.

Clinical Presentation, Diagnosis, and Therapeutic Approach

Skin Manifestations of Intrinsic and Extrinsic Skin Aging

Different manifestations occur in the aging skin: dry skin, telangiectasia, senile purpura,

freckling, lentigines, guttate hypomelanosis, stellate pseudoscars, solar comedones, colloid milia, senile angiomas, focal depigmentation, epidermal atrophy, ephelides, hyperpigmentation, wrinkles, solar elastosis, asperity, actinic keratosis, and loss of elasticity [4, 53, 54, 59, 60, 70, 71] (Figs. 34.3, 34.4, and 34.5).

Fig. 34.3 Guttate hypomelanosis

Fig. 34.4 Actinic keratosis

Fig. 34.5 Senile purpura

Skin Infections in the Elderly

Skin and soft tissue infections are common in the general population and in older persons. Because of changes in skin consistency, immunosenescence, and the presence of underlying skin conditions and comorbid conditions, the elderly are at high risk for skin infections [88]. A number of special conditions and circumstances need to be considered in the diagnosis and therapy. It is important to try to establish the causative organism, exclude other cutaneous disorders, and identify precipitating factors [89].

Bacterial Infections

In the elderly some bacterial infections are frequently acquired in the community, such as cellulitis, erysipelas, necrotizing fasciitis, impetigo, folliculitis, furuncle, ulcerations, and secondary infections. These infections usually present with erythema, blisters, pus-

Box 34.2 Important Note
For any given medical problem, morbidity and mortality are increased by two- to three-fold in the elderly. The elderly population has an increased incidence of pneumonia, urinary tract infections, and skin and soft tissue infections [89]

tules, and ulcerations. Cellulitis and infected ulcers are the most commonly encountered cutaneous infections in the elderly. Accurate and quick diagnosis and treatment are imperative to prevent significant morbidity and mortality [88, 89].

This increased susceptibility to infections has been attributed to a dysregulation and decline of immune function with age, particularly in cell-mediated immunity. The prevalence of Gram-negative bacteria (*Pseudomonas aeruginosa* and *Proteus mirabilis*) colonization of skin is about 25% more frequent in the elderly compared with younger persons. Also, aging is associated with thinning and increased dryness of the skin and a reduced blood flow, therefore increasing the chance of injury and reducing the time to healing. Both malnutrition and obesity are further risk factors for infection and poor wound healing [89].

Infections in the elderly may present with atypical signs and symptoms. Fever is often low-grade or absent. On the other hand, because of delay in presentation, patients may present with septic shock or confusion. Bacterial skin and soft tissue infections may complicate an underlying chronic skin disorder, causing further diagnostic difficulties. Traditionally, therefore, a skin infection is confirmed by taking a swab of the wound surface, which is then sent for bacterial analysis [89].

The principles of treatment of bacterial skin infections in the elderly are the same as for any age group, but there are some important considerations. Absorption, distribution, metabolism, and elimination of drugs are altered in the elderly for a variety of reasons. Increased drug interaction resulting from polypharmacy, comorbidity, and reduced renal function are some of the factors that influence pharmacokinetics. Compliance with treatment may be impaired. The practicalities of some therapies need to be considered. Social circumstances also play an important role, for example if a patient lives alone or is cared for in a long-term residential or nursing home [89].

Cellulitis and Erysipelas

Cellulitis is a bacterial infection of the lower dermis and subcutaneous soft tissue, and is a common condition in the elderly [90]. It occurs frequently in long-term care facilities, affecting 1–9% of residents [89] The majority of cellulitis cases are caused by Gram-positive organisms, most commonly streptococci (group A most commonly, and also groups B, C, and G) and *Staphylococcus aureus* [88, 89]. The organisms often gain entry through broken areas, such as cuts, abrasions, ulcers, fissures caused by dermatophytes, or animal bites [88, 89]. Peripheral lymphedema and venous stasis are also important in the pathogenesis of some cases [88].

Cellulitis presents with ill-defined erythema, pain, and edema. The pain is often worse on palpation and there may be blister formation and exudation. It usually affects the legs, and the draining lymph nodes can be palpable and tender. The skin signs can be accompanied by systemic symptoms including fever, malaise, and confusion. The main differential diagnosis is deep vein thrombosis. Other differentials include allergic contact dermatitis and stasis dermatitis [89].

Erysipelas is an acute infection of the dermis an upper subcutaneous tissue, caused in the majority of cases by β-hemolytic *Streptococcus pyogenes* and less commonly *S. aureus* [89, 90]. The face and legs are the most commonly affected sites, and a search for a portal of entry is important [89].

In erysipelas the skin is bright red, edematous, and often very tender in a unilateral distribution. Characteristically there is a well-demarcated advancing border, and vesicles and bullae may be present on an advancing margin. A classic sign is the orange-peel appearance. Malaise and fever are frequent accompanying symptoms. In the elderly, erysipelas can present abruptly as a toxic confusional state. It is not always possible to distinguish clinically between cellulitis and erysipelas [89].

The management of cellulitis and erysipelas is similar, and antimicrobial therapy should include agents that are effective against streptococci and *S. aureus*. Typical agents include penicillins,

penicillinase-resistant penicillin, or oxacillin for 10 days [88, 89]. Vancomycin and clindamycin can also be used [88]. Patients with penicillin allergy should be given erythromycin, tetracycline, or a first-generation cephalosporin. Depending on the severity of the signs and symptoms, treatment can be given either orally or parenterally. A response to the treatment should be seen within 48 h [88, 89]. Elevation of the affected area (e.g., a lower extremity) helps to decrease edema by promoting lymph and venous drainage, and can accelerate the time from treatment initiation to cure [88] (Fig. 34.6).

Necrotizing Fasciitis

Necrotizing fasciitis is a rare but severe infection of the subcutaneous tissue that tracks along the fascial layers, usually destroying the superficial fascia. It usually develops after a superficial injury such as an insect bite, abrasion, or cut [88]. It is an especially destructive infection causing rapidly advancing deep tissue necrosis. It may be caused by a number of organisms, either in isolation or more commonly as polymicrobial infection, including facultative bacteria and anaerobes such as *Klebsiella* spp. and *Pseudomonas aeruginosa* [89].

There are two types of necrotizing fasciitis. Type 1 is a polymicrobial infection and usually follows a surgical procedure. Other predisposing factors are pressure ulcers, perianal abscess, intravenous drug abuse, Bartholin abscess, or other vulvovaginal infection. Pathogens typically include a mix of aerobic and anaerobic Gram-positive and Gram-negative bacteria. Frequently,

patients have a history of diabetes mellitus. It often occurs in the lower extremities, abdominal wall, groin, or perianal region. Type 2 is a mono-microbial infection most commonly caused by *S. pyogenes*. It usually occurs in the lower extremities, and the predisposing factors include diabetes mellitus, peripheral vascular disease, herpes zoster, blunt trauma, intravenous drug abuse, childbirth, and surgery [88].

Rapid diagnosis and treatment are essential for this potentially fatal condition. The hallmark of treatment is surgical intervention. Surgical drainage and exploration is warranted if local wounds demonstrate necrosis or easy dissection along fascial planes. Antimicrobial therapy is a useful adjuvant to surgical debridement and should be directed against suspected pathogens, both aerobic and anaerobic [88].

Impetigo

This superficial cutaneous infection is caused by *S. aureus* or β-hemolytic group A streptococci. There are two classic forms of impetigo: a non-bullous variant (70% of cases) and a bullous variant. Patients develop pustules and blisters, which then form honey-colored yellowish crusts. Lymphadenopathy and leukocytosis are frequent associated findings. It often occurs around the mouth and nose as well as wounds. Is very contagious, and contacts should be examined [89].

Treatment should comprise topical or systemic antimicrobials. The localized area of impetigo can be treated with topical fusidic acid or mupirocin for 7–10 days. However, a widespread infection requires systemic drugs: oxacillin, erythromycin, or cephalosporin for 10 days. Crusts need to be removed with the aid of warm saline or antibacterial cleansers [89].

Folliculitis and Furuncles

Folliculitis is a superficial infection of the pilosebaceous follicle, usually in areas with short coarse hair such as the neck, beard area, buttocks, and thighs. It is most commonly caused by *S. aureus*. Multiple small erythematous papules and pustules develop surrounding a hair. There may be some pain or itching. Mild localized folliculitis may resolve without treatment. Mostly a topical anti-

Fig. 34.7 Folliculitis

bacterial such as fusidic acid, erythromycin, or mupirocin may be necessary. Oral antibacterials (oxacillin, penicillin-clavulanic acid, or erythromycin) are necessary for more extensive and severe cases. Testing for antibacterial sensitivity with a skin swab is recommended [89].

Furuncles develop when a deeper infection of the hair follicle occurs with *S. aureus*. They are usually tender and heal with scarring [90]. Typically, a furuncle involves an inflammatory nodule overlying a pustule [89]. Predisposing factors include scabies, excoriations, diabetes mellitus, obesity, malnutrition, and the use of corticosteroids and immunosuppressive drugs [89]. Treatment includes drainage of purulent lesions, application of moist heat to promote natural drainage, and antibiotics. Oral oxacillin is the drug of choice for this infection [88, 89] (Fig. 34.7).

Secondary Infections
Excoriations or scratch marks can be caused by a variety of dermatologic problems, such as eczemas, infestations, mycosis, drug reactions, psoriasis, and autoimmune blistering diseases. Pruritus can also be a symptom of systemic conditions such as diabetes mellitus, renal and hepatic impairment, hematologic diseases, thyroid disorders, and neoplasms. These conditions cause itching and the scratch marks often show signs of exudate and crusting because of secondary infection, most commonly caused by *S. aureus* [89].

Other conditions can develop secondary infections, such as pressure ulcers, leg ulcers (arterial or venous), and surgical sites [88].

Hanseniasis
Hanseniasis (Hansen's disease) is a systemic infectious disease caused by *Mycobacterium leprae*, an intracellular and acid-fast bacteria that primarily affects the skin and peripheral nerves. It is a public health problem because of its potential to incapacitate, and is a compulsory reporting disease worldwide.

Diagnosis is mainly clinical, based on a good anamnesia and physical examination of the skin and nerve trunks. Multidrug therapy (MDT), a combination of two (rifampicin and dapsone) or three (rifampicin, dapsone, and clofazimine) drugs is effective in treating hanseniasis and to prevent physical disabilities and deformities relevant to the disease.

In the elderly, some considerations about clinical manifestations, diagnosis, and treatment are appropriate. According to the WHO, hanseniasis should be suspected in individuals with any of the following symptoms or signs [90]: pale or reddish patches on the skin; loss or decrease of feeling in the skin patch; numbness or tingling of the hands and feet; weakness of the hands, feet, or eyelids; painful or tender nerves; swelling or lumps in the face or ear lobes; painless wounds or burns in the hands or feet.

The elderly, however, because of the physiologic aging of the nervous system and skin, present natural decrease of skin sensations resulting from changes that occur in the organs of the senses. The same can be inferred with respect to muscles, which show a decrease in the number and diameter of the muscle fibers leading to progressive sarcopenia and muscle weakness [11]. With respect to thinning of the eyebrows that occurs in hanseniasis, Eidt [87] found that 40.1% of the elderly have thinning eyebrows without infection by the Hansen bacillus.

Regarding treatment with MDT, it is important to consider the decrease in hepatic and renal function [11] and the risks of polypharmacy and adverse drug reactions in the older population [91] (Fig. 34.8).

Fig. 34.8 Hanseniasis

Viral Infections

The diagnosis and management of viral diseases of the skin are significant issues in the elderly population. It is important for clinicians to monitor and treat these diseases aggressively because of the potential for immunosuppression in this population [92, 93]. Herpes zoster and postherpetic neuralgia are two of the major topics of interest in the geriatric population.

Herpes zoster is caused by reactivation of the varicella zoster virus (VZV) that causes chickenpox in children, and is primarily a disease of older adults. After acute varicella infection, VZV becomes latent in the dorsal root ganglia. An unknown trigger mechanism, possibly caused by declining or impaired cell-mediated immunity, results in a reactivation of VZV [92, 93].

In immunocompetent persons, herpes zoster is usually confined to a single dermatome, and cutaneous or visceral dissemination is rare. Herpes zoster is also associated with a characteristic pain syndrome: prodromal pain (occurs before the rash and vesicles), acute pain (occurs throughout the course of vesicular eruption), and chronic pain or postherpetic neuralgia (can last from months to years after the disappearance of the herpes zoster lesion) [92, 93].

Antiviral therapy is aimed at decreasing viral replication, thereby lessening nerve damage or inflammation, and reducing the duration and severity of long-term pain syndromes. The benefits of antiviral therapy in reducing the extent and duration of pain have been seen in patients older than 50 years of age, reflecting the age-related association of long-term pain. To be effective, antiviral therapy must be instituted early, usually within 72 h of the onset of the rash [92, 93].

For many years, acyclovir was the gold standard for the treatment of herpes zoster. It is used at 800 mg five times a day for 7 days. In immunosuppressed patients therapy should be continued until new lesions stop forming and those that have formed crust over. Acyclovir remains one of the safest agents. Other drug dosages include famciclovir 500 mg three times a day for 7 days, and valacyclovir 1 g three times a day [92, 93].

Postherpetic neuralgia should be treated with topical lidocaine-prilocaine cream or 5% lidocaine gel. These drugs can be used intravenously or as local injections. Oral aspirin has limited value. Ibuprofen is ineffective. Topical capsaicin is not recommended, even it is approved by the US Food and Drug Administration, because the burning elicited during its application is intolerable. Tricyclic antidepressant drugs are useful: phenytoin and sodium valproate have been reported to reduce pain. Carbamazepine reduces lancinating pains but is ineffective for continuous pain. However, the best choice for the management of postherpetic neuralgia is its prevention, and trials have shown that valacyclovir provides an improved benefit over acyclovir [92, 93] (Fig. 34.9).

Fig. 34.9 Herpes zoster

Fungal Infections

Fungal infections are among the most prevalent dermatologic conditions in the elderly, second only to benign and malignant tumors. They are caused by *Malassezia*, *Candida*, *Trichophyton*, *Microsporum*, *Epidermophyton*, and rarely by *Scopulariopsis*, *Fusarium*, and *Aspergillus* [94].

Diagnosis can be confirmed by potassium hydroxide preparation (KOH) with direct microscopy or fungal culture. Dermatophyte infections respond to griseofulvin, terbinafine, and azoles (ketoconazole, itraconazole, fluconazole). Nondermatophyte molds are more difficult to treat and may require combination therapy, but they are not common in the elderly.

Candidiases

Candida is part of the normal microflora and can be isolated from all healthy individuals. The development of an infection depends on the balance between the pathogenicity of the yeast and the host immune defenses. Predisposing factors more common in the elderly include systemic infections, malignancy, diabetes, vitamin deficiency or malnourishment, denture use, and use of broad-spectrum antibiotics and corticosteroids (inhaled, topical, systemic) or other immunosuppressive agents [94].

Candida albicans is the most common fungal infection of the oral cavity. Oral candidiasis has a variety of clinical presentations including thrush or pseudomembranous candidiasis, atrophic candidiasis, and angular cheilitis. Topical antifungal creams effective against yeast include ketoconazole, econazole, and ciclopirox olamine. In general, twice-daily application for a few weeks is effective [94].

C. albicans thrives in warm, moist environments provided by intertriginous sites including axillary, inframammary, inguinal, perianal, and interdigital areas. Predisposing factors include obesity, diabetes immunosuppression, maceration, and chronic debilitation. The affected areas are treated with topical ketoconazole, econazole, oxiconazole or ciclopirox olamine twice daily for 2–4 weeks. Topical terbinafine cream is not effective against yeasts [94] (Fig. 34.10).

Fig. 34.10 Interdigital candidiasis

Candida is a normal inhabitant of the vaginal tract that behaves as a pathogen when the host immune response is impaired. Predisposing factors for vulvovaginitis in elderly women are diabetes and the use of broad-spectrum antibiotics. Topical treatments include miconazole, nystatin, and clotrimazole. Fluconazole and itraconazole are systemic options. Single-dose oral fluconazole, 150 mg, is probably the most convenient option [95]. *Candida* causing balanitis or balanoposthitis can be treated with the application of topical azoles twice daily [94].

Paronychia by *Candida* is associated with frequent wetting of the hands. Therapeutic options include application of topical azole twice daily for 4–6 weeks or systemic azoles (fluconazole or itraconazole). Avoiding frequent exposure to water is recommended to prevent recurrent infection [94].

Dermatophytoses

Dermatophyte infections can occur on the scalp (tinea capitis), trunk (tinea corporis), intertriginous sites (tinea cruris), hands (tinea manuum), feet (tinea pedis), and nails (onychomycosis). Tinea capitis is overwhelmingly an infection of children and only occasionally affects the elderly.

Tinea pedis, or athlete's foot, is the most common of the dermatophyte infections [94] and should be a predisposing factor for erysipelas and cellulitis in the elderly. Patients with tinea pedis should also have other locations examined, such as nails, hands, and groin, which can be a source of the infection. Tinea pedis has three

Fig. 34.11 Tinea corporis

characteristic clinical presentations: interdigital, moccasin-type, and vesiculobullous. Successful management includes antifungal therapy and prevention of reinfection. Any of the topical azole creams or terbinafine cream applied twice daily for 2–4 weeks is usually adequate. Oral therapy is more practical for elderly patients with poor vision or difficulty reaching their feet. However, terbinafine, itraconazole, or fluconazole require careful review of the patient's medication list to identify potential drug interactions [94] (Fig. 34.11).

Onychomycosis

Onychomycosis is caused by dermatophytes in the majority of cases (9%), but can be caused by *Candida* (2%) and nondermatophyte (8%) molds [95]. It is found more frequently in the elderly, more so in males than females [2–94].

> **Box 34.3 Important Note**
> Because of impaired host defenses and a favorable environment of specific anatomic sites, there is an increased prevalence of mucosal and cutaneous candidiasis, tinea pedis, and onychomycosis in the geriatric population compared with other age groups.

The four types of onychomycosis are distal subungual, proximal ungual, white superficial, and *Candida* onychomycosis. Despite the clinical impression, it is recommended that onychomycosis should be confirmed by mycologic examination whenever possible [92, 93]. The management of onychomycosis is done with terbinafine or itraconazole, both of which are effective. Ciclopirox lacquer should be useful in patients who are not candidates for systemic therapy, although it has significantly lower efficacy than the oral medications [92–94].

Cutaneous Parasitosis

With the geriatric population on the rise, different kinds of institutions for the elderly have been built, such as assisted-living facilities and nursing homes. Because of these living arrangements, however, this population is at a risk for infectious diseases, particularly scabies and pediculosis [95].

Scabies

In the United States scabies has caused major problems in nursing homes, particularly in debilitated patients. The risk factors include age of the institution (more than 30 years), size of the institution (more than 120 beds), and the ratio of beds to healthcare workers (more than 10:1) [95].

Patients show signs of infection after about 2 weeks. Patients who have been previously infected develop the symptoms 1–4 days after being reinfected. The burrows are present as lesions with a short elevated serpiginous track. A small papule may appear at the end of the burrow or occur independently. The burrows and the papules occur on hands, interphalangeal finger webs, wrists, waistline, and anterior and posterior axillary folds. They can also be found on the external genitalia, nipples, and buttocks [95].

Scabies can exist in different forms: nodular, bullous, and crusted or keratotic scabies. The crusted or "Norwegian scabies" usually infects immunocompromised patients, which leads to decreased inflammatory reaction, hence decreased pruritic presentation. In patients with keratotic scabies, HIV status should be determined. The diagnosis is relatively easy and clinical. Early diagnosis is important in preventing secondary infection and potential epidemic outbreaks. One of the treatments of choice is 5% permethrin cream. Another possibility is systemic ivermectin [95] (Fig. 34.12).

Fig. 34.12 Scabies

Fig. 34.13 Pediculosis

Pediculosis

Pediculosis, or lice, is an infestation of the hairy parts of the human body or clothing with eggs, larvae, or adult lice. Being host specific, the human lice cannot be transmitted to or from pets or other mammals. There are two species of lice that infest humans: *Pediculus humanus* and *Phthirius pubis* [95].

P. humanus is further divided into subspecies, *P. humanus capitis* (head louse) and *P. humanus corporis* (body louse). *Pediculosis capitis* is an infestation of lice on the scalp. Lice are transmitted through direct contact between individuals or indirectly by contacts with bedding, clothes, or brushes. The lice survive by sucking blood from the scalp. The diagnosis is based on clinical presentation, such as detection of nits or lice, and can be confirmed by using a Wood's lamp [95].

Pediculosis corporis infects the body. The lice and nits are seen in clothing and bedding. Infestation is caused by poor hygiene. Sites of feeding present as red maculae, papules, or popular urticaria with central hemorrhagic punctum [96].

Pediculosis pubis (phthiriasis) (more commonly known as "crabs") is located in the pubic region. Pubic lice are typically transmitted sexually, and frequently coexists with other sexually transmitted infections [95].

In general, there are many effective treatments for lice. Cream or lotion with 5% permethrin is safe and effective. Reapplications are recommended 7–10 days later. Despite common practice, shampoo should be avoided. It is ineffective because of short contact time and low drug concentration. Oral ivermectin requires a second dose 10 days later. All contaminated items should be decontaminated, such as combs, clothing, hair brushes, hats, and clothing [95] (Fig. 34.13).

Xerosis

Skin barrier integrity depends on complex interactions between the corneocytes embedded in the cornified envelope consisting of crosslinked proteins, filaggrin, and lipid bilayers. Numerous factors may predispose to xerosis, including external aggressions, climate, medication, malignant diseases, endocrine disorders, infections, and renal failure in dialyzed patients. Another factor is aging, which is associated with modifications in skin hydration and barrier function properties, accounting for an increased risk of xerosis [96].

Xerosis is a common skin manifestation in the elderly. Some epidemiologic studies, mostly conduced in nursing homes, have shown a prevalence of xerosis in older people ranging from 30% to 75% [96]. Predisposing factors are the use of cosmetic agents containing soap or detergents, the use of perfumes, and the use of keratolytic agents. Associated factors are older age, female sex, current or previous history of atopic dermatitis, dry skin during childhood or adolescence, and itching during sweating.

Fig. 34.14 Xerosis

The management of xerosis should include avoiding the predisposing and associated factors and using moisturizers, emollients, and barrier creams. Topical therapies with a low pH may be especially useful in optimizing the skin barrier function through their maintenance of the normal acidic pH of the skin surface [97] (Fig. 34.14).

Pruritus

The most common skin complaint in the elderly is pruritus. In advanced age pruritus can result from a variety of etiologies, although xerosis is the most common. In addition, certain cutaneous and systemic diseases associated with pruritus are more prevalent in the elderly [97].

As skin ages, the tegumentary and vascular systems undergo atrophy, leading to suboptimal moisture retention. However, many elderly patients have pruritic skin without xerosis. Other skin changes in advanced aged patients that may contribute to itch include decreased skin surface lipids and clearance of transepidermally absorbed materials from epidermis, reduced sweat, and sebum production, as well as diminished barrier repair.

A decline of normal immune function that occurs with aging also produces a higher incidence or autoimmune skin disorders that can induce pruritus, such as bullous pemphigoid and postherpetic neuralgia. Age-related changes in nerve fibers and polypharmacy may also be involved. Certain cutaneous and systemic disorders that are associated with pruritus are also more prevalent in patients of advanced aged. However, in many cases no apparent cause is found [97].

Certain pruritic cutaneous diseases are more prevalent in the elderly population, such as xerosis, nummular dermatitis, and seborrheic dermatitis; the latter is common in patients with dementia and Parkinson's disease. Systemic diseases that are associated with pruritus, such as chronic kidney disease, hepatic dysfunction, and endocrine disorders, are also more prevalent in the elderly [97].

Notably, infectious etiologies of pruritus, including scabies and lice, may be more common in this age group, especially within institutionalized care settings. In addition, medications used by old people, such as aspirin and angiotensin-converting enzyme inhibitors, increase the possibility of drug-induced pruritus. Another important consideration is that chronic pruritus may be a presenting sign of underlying malignancy, such as lymphoma and multiple myeloma. Psychogenic and neuropathic disorders are also common in the elderly. Once cutaneous and systemic causes of itch are excluded, idiopathic itch of the elderly may be considered [97, 98].

A detailed history, review of systems, and physical examination are of prime importance in guiding antipruritic treatment of senescent skin. Some measures may be useful in the management of pruritus in the elderly irrespective of the underlying cause. As there is no universally accepted therapy for itch, patient education is important in the management of pruritus. It is also important to consider the physical and cognitive impairments of the elderly [97].

Identifying and removing aggravating factors are often the initial steps in effective treatment. Breaking the "itch-scratch" cycle is critical, and patients should be informed of the increased cutaneous inflammation caused by scratching. Some measures, such as keeping fingernails short, wearing light and loose clothing, maintaining a comfortable temperature, and using moisturizers or barrier creams regularly, are essential. Restricting time in the shower or bathtub and avoiding cleansers is also important [97].

Whenever possible, simple topical regimens are preferable in order to limit potential adverse drug reactions. Topical treatments include moisturizers, emollients, and barrier creams. These nonpharmacologic compounds reduce pruritus through improving barrier function and prevent-

ing the entry of irritants. Topical corticosteroids do not exert an antipruritic effect and should be used only when itching is associated with inflammatory skin diseases. Topical immunomodulators (tacrolimus and pimecrolimus) have been shown to be effective in reducing pruritus in chronic conditions [97].

Elderly patients report a reduction in pruritus with topical therapies containing menthol (1–3%). Capsaicin has been reported to have a beneficial effect in chronic localized pruritic disorders, but the intense burning sensation may lead to poor compliance in the elderly. Local anesthetics (pramoxine, polidocanol) reduce pruritus significantly. Topical salicylic acid has also been shown to reduce pruritus.

The antipruritic mechanism of systemic treatments such as antidepressants (mirtazapine, paroxitine, sertraline) is unclear, but they seem to reduce the perception of pruritus at the cortex. With the exception of chronic urticaria, antihistamines have little effect on conditions associated with pruritus, and in the elderly care must be taken to avoid causing excessive drowsiness and falls. Opioid agonists and antagonists (naltrexone) and neuroleptics (gabapentin, pregabalin) can also be used, but their antipruritic effects are not clear. Another possible treatment is phototherapy (ultraviolet A and narrowband B) [97] (Table 34.1).

Table 34.1 Systemic diseases accompanied by generalized pruritus

Liver diseases	Primary biliary cirrhosis
	Primary sclerosing cholangitis
	Extrahepatic cholestasis
	Hepatitis B and C
Kidney diseases	Chronic kidney insufficiency
Hematologic diseases	Polycythemia vera
	Hodgkin disease
	Non-Hodgkin lymphomas
	Leukemias
	Myeloma multiplex
	Iron deficiency
	Systemic mastocytosis
	Hypereosinophilic syndrome
	Myelodysplastic syndromes
Endocrine disorders	Diabetes
	Hyperthyroidism
	Hypothyroidism
	Hyperparathyroidism
Neurologic diseases (neuropathic pruritus)	Brain injury/tumor (frequently unilateral pruritus)
	Sclerosis multiplex
	Small fiber neuropathy
Solid tumors (paraneoplastic tumors)	
Carcinoid syndrome	
Infectious diseases	HIV infection/AIDS
	Infestations

Adapted from Cardona et al. [98]

Eczemas

Eczema is common in the older population. Age-related changes predispose to an increased burden of dermatitis, which is thought to be due to impaired barrier function. There is an increased prevalence of asteatotic and venous eczema, although atopic eczema is less common [99]. A number of factors in older subjects contribute to their risk for developing allergic-related conditions. These include frailty, coexisting medical problems, memory issues, use of multiple prescribed and nonprescribed medications, and skin aging, which results in a progressive loss of function and structural integrity, leading to impaired immune response and skin barrier function [98]. The management of the elderly with eczema involves various aspects: it is important to establish the time of onset the eczema, its pattern and severity, response to previous treatments, possible trigger points including medications, and the impact on quality of life. In the elderly population, eczema may be linked to systemic disease [99].

The most common types of eczema to affect older people are asteatotic eczema and venous/stasis eczema. However, any of the other types of eczema can occur: contact dermatitis, seborrheic dermatitis, eczematous drug eruptions, and atopic eczema [99]. Seborrheic dermatitis is more prevalent in older people, especially in those confined to bed [99] and in those with neurologically associated pathologies [100]. Elderly patients may develop allergic contact dermatitis despite the fact that cell-mediated immunity is decreased as a result of unknown mechanisms [98, 101].

The recommended management of eczema in older patients should be kept simple. Options for the

treatment of eczema include topical and systemic drugs, and topical treatments may prevent major adverse effects. Emollients are fundamental to restoring the barrier, and their correct use will reduce the need for topical steroids. Topical steroids are effective at clearing eczema, but they are safe for short-term use, although they should be prescribed with caution in older patients because of the risk of side effects and to prevent tachyphylaxis [99, 102].

Topical immunomodulators have a potent anti-inflammatory effect, and the patient should be warned that this may cause a transient sensation of warmth and burning. Elderly patients are at risk of secondary bacterial infection, and in such cases antibiotics must be given. Besides these measures, adequate education for self-care and emotional support are essential [98, 99] (Figs. 34.15, 34.16, and 34.17).

Fig. 34.17 Contact dermatitis

Fig. 34.15 Contact dermatitis

Fig. 34.16 Stasis eczema

Pressure Ulcers

Pressure ulcers are defined as skin lesions, underlying tissue, or both, resulting from extrinsic pressure applied to the body surface and presenting multifactorial etiology [36]. Approximately 70% of pressure ulcers occur in individuals over the age of 70 years [103].

There are numerous risk factors that put the elderly at higher risk for skin breakdown. These factors can be classified as intrinsic or extrinsic. Intrinsic factors are those that influence the architecture and integrity of the skin's supporting and underlying structures. They include limited mobility or immobility; comorbidities, such as diabetes, chronic obstructive pulmonary disease, congestive heart failure, malignancy, and renal dysfunction; poor nutrition; and aging skin. Extrinsic factors are those that influence tissue tolerance by impinging on the skin surface. They include pressure, friction, shear stress, and moisturizing [103, 104].

The management of pressure ulcers can be divided into four stages: pressure relief, debridement, management of bacterial load, and selection of a topical dressing [103] (Figs. 34.18 and 34.19).

Fig. 34.18 Pressure ulcer

Fig. 34.20 Basal cell carcinoma

Fig. 34.19 Pressure ulcer

Malignant Dermatosis

With the significant increase in the average life span worldwide, skin cancer has become a great health concern [105], given that the number of aged patients with cutaneous cancer will increase in coming years [106]. There are various epidemiologic, biological, and molecular data suggesting that skin cancer is predominantly a disease of the elderly, since approximately 53% of skin cancer-related deaths occur in persons older than 65 years [107].

There are three principal types of skin cancer. Basal cell carcinoma represents 68.2% of all cutaneous cancer in aged people, squamous cell carcinoma 23.5%, and melanoma 3.25% [107]. Another study found an incidence of melanoma of 1.4% in patients older than 60 years [108].

With regard to the management of elderly patients with skin cancer, this should be individualized depending upon the clinical performance status, and the age alone should not constitute an obstruction for the administration of the optimal treatment. Since elderly patients with melanoma have a worse prognosis, emphasis should be laid on primary and secondary prevention. Physicians treating elderly patients should be trained to employ an individualized approach to these patients and encouraged to participate in programs for the early detection of suspicious skin lesions [105] (Figs. 34.20 and 34.21).

Fig. 34.21 Squamous cell carcinoma

Box 34.5 Important Note
The geriatric patient is at high risk of developing cutaneous neoplasms, especially carcinomas.

Skin Manifestations of Systemic Diseases and Disorders

The aging process carries the risk of longevity becoming a pathologic form and accompanied by chronic disease. About 85% of elderly Brazilians have at least one chronic illness and about 15% have at least five [109]. These data reinforce the importance of paying attention to the skin of the elderly and drawing the association between cutaneous lesions and internal diseases.

Disorders of the every organ system may cause skin symptoms and signs, some of which are due to the treatment of these conditions. Skin manifestations of systemic diseases are wide, varied, specific, and nonspecific. Generalized pruritus and cutaneous vasculitis are more common skin presentations when an underlying disease may be present, and will influence management [110].

The skin may be the demonstration site of various internal diseases. Pathologies of metabolic and nutritional origin, and endocrine, neurologic, pulmonary, cardiac, gastrointestinal, genitourinary, and renal diseases may have skin lesions that contribute to their diagnosis.

In certain chronic disease such as connective tissue disease and chronic liver disease there are characteristic cutaneous findings. Internal malignancies such as multiple myeloma may present with distinctive cutaneous findings, which need to be recognized to institute a search for the underlying neoplasm [110].

Xanthomas, yellowed skin lesions characterized by cholesterol or triglycerides deposited on the skin, can change the cholesterol metabolism indicator. These lesions may also occur in hepatic disease, diabetes, and myxedema [111].

Cardiopulmonary diseases may be manifested by cyanosis and enanthema (cyanosis of mucous membranes), erythema, digital clubbing, premature male pattern baldness, xanthomas, and diagonal crease in the earlobes. Pulmonary diseases can be associated with atopic dermatitis, skin mycoplasma infections and tuberculosis, and larva migrans infestation [112].

Chronic liver disease is associated with a number of cutaneous manifestations. Any patient with hepatic dysfunction may have multiple spider nevi, palmar erythema, acquired ichthyosis, or macular purpura in association with a coagulopathy. Cholestasis may be associated with jaundice and generalized pruritus, which can result in secondary lesions such as escoriations and prurigo nodules [110].

Diabetes mellitus (DM) is a metabolic disease that predisposes patients to several other diseases, notably cutaneous ones. The cutaneous alterations of DM are therefore subdivided into four groups: lesions strongly associated with DM, cutaneous infections, reactions to medications, and diabetic food [113]. The lesions strongly associated with DM are necrobiosis lipoidica, annular granuloma, Kyrle's disease, scleredema of Buschke, bullosis diabeticorum,

eruptive xanthomas, generalized congenital lipodystrophy, and pseudoacanthosis nigricans.

The metabolic alterations of DM are responsible for the comparison between the diabetic patient and the immunocompromised, so the diabetic patient is more susceptible to cutaneous infections. Pyoderma and abscess occur with greater severity. The same occurs with fungus infections, including those caused by dermatophytes and candidiasis, especially the genital form [113].

The reactions to medications may be associated with the use of insulin or oral hypoglycemics. The skin manifestations due to insulin are insulin edema, insulin lipodystrophy, or hypertrophy and insulin allergy. Secondary reactions to the use of oral hypoglycemics include cutaneous eruptions, Stevens-Johnson syndrome, exfoliative dermatitis, photosensitivity, lichenoid eruptions, and antabuse effect [87, 113]. The diabetic foot occurs harbors numerous clinical variants: plantar neurotrophic ulcer, microangiopathic ulcer, superficial and deep infections, and ischemic lesions by truncal arteriopathy [113].

In hypothyroidism the patient presents with dry and rough skin, sometimes simulating ichthyosis vulgaris. Occasionally hyperkeratosis develops on the palms and soles (palmoplantar keratoderma). The skin may appear cool, waxy, pale, and swollen, sometimes with a yellow color caused by carotenemia. Fingernails become coarse and easily break. Coarse, brittle hair or diffused alopecia may be present [87].

The most common manifestations of hyperthyroidism include warm and moist skin, palmar erythema, fine and friable scalp hair with alopecia, and onycholysis. Thyroid dermopathy is known as pretibial myxedema and tends to be bilateral. However, this condition occurs in only 3% of patients [87].

Vitamin and nutritional deficiencies are common in the elderly population. It has been estimated that as many as 55% of hospitalized elderly and up to 85% of institutionalized old persons are undernourished. The early manifestations of vitamin C deficiency (scurvy) are nonspecific, such as malaise and weakness. Skin lesions include perifollicular hemorrhage, petechiae, gingival bleeding, and splinter hemorrhages. The initial manifestations of niacin deficiency (pellagra) are nonspecific and the classic triad of dermatitis, dementia, and diarrheas is seen only in advanced cases. The dermatitis is bilateral, symmetric, and is seen in sun-exposed areas secondary to photosensitivity, which begins with symmetric itching and painful erythema on the back, neck (Casal's necklace), face, and dorsum of the hands. Vesicles and bullae may erupt leaving crusty, scaly lesions [87].

Vitamin A deficiency has been associated with dry skin, follicular hyperkeratosis, and poor wound healing. Zinc deficiency is noted as patches and dry, scaly, sharply defined, and deep red plaques. Lesions initially appear in the perioral and anogenital areas, with later involvement or the scalp, hands, feet, flexural regions, and trunk. In the elderly population the common associated factors are malignancies, chronic kidney disease, certain drugs (penicillamine, diuretics) and long duration of total parenteral nutrition therapy [87].

Adverse Drug Reactions

Age-associated multimorbidity often results in polypharmacy and elevates the risk of adverse drug reactions. Decisive alterations in pharmacokinetics and pharmacodynamics are detectable in old age. Primarily a decrease in total body water, an altered ratio of muscle mass to fat tissue, decreased renal function, and change in hepatic drug metabolism all potentially cause drug-related complications [114].

The cutaneous manifestations of adverse drug reactions are produced, directly or indirectly, by various mechanisms and triggered by the use of drugs. The drugs more frequently involved are sulfa, antibiotics, analgesics, anti-inflammatories, and sedatives [115]. Drugs most commonly implicated in type I, II, and III hypersensitivity reactions in older patients include β-lactam drugs, nonsteroidal anti-inflammatory drugs, quinolones, trimethoprim-sulfamethozaxole, nitrofurantoin, heparin, neuromuscular blocking agents, antiepileptics, chemotherapeutic agents,

monoclonal antibodies, and immunosuppressive drugs. On the other hand, systemic drugs most commonly implicated in causing type IV reactions are antiepileptics, allopurinol, dapsone, abacavir, and nevirapine [98].

Various cutaneous manifestations are suggestive of adverse reactions to drugs and can be observed with relative frequency in elderly users of various drugs (polypharmacy). Eczema, fixed pigmented erythema, atrophy, acneiform rash, photosensitivity, photo-onycholysis, acquired ichthyosis, dyschromias, and purpuric lesions are common in this group [115]. The adverse drug reactions can still be manifested as important clinical presentations such as lupus-like erythematosus, dermatomyositis, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative erythroderma, vasculitis, urticaria, vesiculobullous rash, anaphylactic shock, serum sickness, porphyria, pemphigus, photodermatitis, erythema multiforme, erythema nodosum, drug hypersensitivity syndrome, lichenoid and psoriasiform eruptions, and acute generalized exanthematous pustulosis [99].

The evaluation of a potential adverse drug reaction in the elderly may include a thorough history, skin tests (prick or intradermal test or patch tests) and in selected cases challenge tests. However, it is important to evaluate the extent of comorbidity and functional impairment that is present in the elderly patient prior to the initiation of a drug allergy study [98] (Fig. 34.22).

Fig. 34.22 Fixed pigmented erythema

Polymedication or polypharmacy is a limitation in drug allergy assessment. Older ambulatory patients use approximately three times as many medications as younger patients. Hence, the use of large numbers of medications by older patients increases the likelihood of harmful drug interactions, adverse drug reactions, and drug allergies [98].

Glossary

Extracellular matrix Extracellular matrix (ECM) macromolecules are important for creating the cellular environments required during development and morphogenesis.

G_1 phase cellular growth The first growth period of the cell cycle, during interphase, in which the cell grows and cytoplasmic organelles are replicated.

Glycosaminoglycans Structures from the extracellular matrix responsible for maintaining and supporting collagen, elastin, and turgidity (bounce) in the cellular spaces and keeping protein fibers in balance.

Metalloproteinases Metalloproteinases or matrix metalloproteinases (MMPs), collectively called matrixins, are proteinases that participate in ECM degradation. These proteinases play a central role in many biological processes, such as embryogenesis, normal tissue remodeling, wound healing, and angiogenesis, and in diseases such as atheroma, arthritis, cancer, and tissue ulceration.

S_1 phase cellular growth Part of the cell cycle in which DNA is replicated, occurring between G_1 phase and G_2 phase.

Tachyphylaxis The continued or repeated exposure to a drug that may lead to a weakened pharmacological response.

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Skin Manifestations of Major Diseases in Public Health

Cutaneous Manifestations in Diabetes Mellitus

35

Karen Regina Rosso Schons

Key Points

- The most common skin manifestations in diabetes are cutaneous infections, xerosis, and inflammatory skin diseases
- Necrobiosis lipoidica may be viewed as the prototype of a diabetes-associated skin disease
- Granuloma annulare has a marked association with systemic diseases, particularly diabetes and rheumatic diseases
- Acanthosis nigricans has better outcomes with weight reduction and optimal blood glucose control
- Foot ulcerations are one of the most serious and disabling complications of diabetes and are the most common cause of nontraumatic foot amputation
- Patients with diabetes are more prone to infections than healthy individuals

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General Epidemiology

Diabetes mellitus (DM) is a metabolic disorder affecting various organ systems, including the skin [1]. It involves a relative or complete insulin deficiency that leads to alterations in glucose, fat, and protein metabolism. In type 1 DM, insulin insufficiency results from a gradual, immune-mediated destruction of pancreatic β islet cells [2]. It is characterized by abrupt onset, insulin deficiency, a tendency to progress to ketoacidosis even in the early stages, and a dependence on exogenous insulin for survival [3]. In contrast, in type 2 DM, chronic hyperglycemia mainly results from end-organ (particularly the liver and skeletal muscles) insulin resistance. This condition is accompanied by a progressive, age-related decrease in pancreatic insulin release. A genetic predisposition and a strong association with obesity exist for type 2 DM [2].

DM is a rapidly growing pandemic. Around 415 million people worldwide, or 8.8% of adults, are estimated to have diabetes. If these trends continue, by 2040 some 642 million people, or one adult in ten, will have diabetes. Approximately 5.0 million adults died from diabetes in 2015, equivalent to one death every 6 s [4]. In addition, DM is the leading cause of new cases of blindness among adults [5].

Table 35.1 Dermatologic manifestations related to diabetes mellitus

Specific	Nonspecific	Complications
Diabetic dermopathy	Skin tags	Diabetic foot syndrome
Necrobiosis lipoidica	Rubeosis faciei	Cutaneous infection
Granuloma annulare	Yellow skin	Diabetic hand syndrome
Acanthosis nigricans	Xerosis	
Diabetic bullae	Pruritus	
Scleredema diabeticorum	Psoriasis	
Kyrle's disease	Vitiligo	
	Lichen planus	

Cardiovascular disease, kidney failure, and limb amputation also occur more often as a result of DM than from any other disease in the majority of high-income countries [4].

Complications related to diabetes are the result of metabolic, hormonal, environmental, and genetic factors manifesting in every organ system. The cutaneous manifestations range widely in severity (from mundane cosmetic concerns to life threatening), prevalence, and treatment response [6].

Skin disorders may be present in 30–79.2% of people with diabetes, and can occur as the first sign of diabetes or may develop at any time over the course of the disease [7–9]. The most common skin manifestations are cutaneous infections (47.5%), xerosis (26.4%), and inflammatory skin diseases (20.7%) [10].

The prevalence of cutaneous disorders seems to be similar between type 1 DM and type 2 DM patients, but type 2 DM patients develop more frequent cutaneous infections and type 1 DM patients manifest more autoimmune-type cutaneous lesions [1].

In this chapter, diabetes-related skin disorders are divided into those specifically or nonspecifically related to diabetes. In addition, skin complications associated with diabetes are also discussed (Table 35.1).

Skin Manifestations

Diabetes-Specific Skin Conditions

Diabetic Dermopathy
Diabetic dermopathy, also known as shin spots, is considered one of the most common cutaneous lesions in diabetes, although it is not pathognomonic of DM [1]. It affects as many as 30–60% of DM patients [2].

Etiopathogenesis
The etiopathogenesis of diabetic dermopathy is unknown but probably represents a post-inflammatory lesion in poorly vascularized skin or a manifestation of microangiopathy [11].

Clinical Presentation
Lesions begin as multiple, discrete, erythematous, coin-shaped macules or annular rings and are prevalent on the shins [2]. Of unknown etiology, its progression is variable and it may fade slowly, leaving a pigmented area without atrophy, or it may resolve completely, with new lesions developing contiguously [5]. It is a dynamic process, with lesions at varied stages present at the same time [6]. The occurrence of lesions correlates with retinopathy, nephropathy, and neuropathy [2, 5]. Macules are asymptomatic and are not directly associated with increased local morbidity [2].

Complementary Examinations
Because the histopathology is relatively nonspecific, a skin biopsy is not necessary [6].

Therapeutic Approach
No treatment for diabetic dermopathy is necessary [2].

Necrobiosis Lipoidica
Necrobiosis lipoidica (NL) has been shown to be associated with multiple systemic diseases,

including sarcoidosis, autoimmune thyroiditis, inflammatory bowel disease, ulcerative colitis, and rheumatoid arthritis. However, its most common systemic underlying disease is diabetes [12].

NL may be viewed as the prototype of a diabetes-associated skin disease. Although it is rare, its prevalence in adult patients is approximately 0.3–1.6%, occurring more frequently in women [3–7].

Most patients with NL will be diagnosed with diabetes at some point in their lives, and type 1 DM is more frequently associated with it [6, 9]. The presence of this disorder in diabetic patients is associated with a higher frequency of retinopathy and nephropathy [3]. Nevertheless, glycemic control has no effect on its course [9, 13].

Etiopathogenesis

The cause of NL remains unknown. The leading theory involves microangiopathy as a result of glycoprotein deposition in the vasculature, resulting in the thickening of blood vessels [13].

Clinical Presentation

The presence of NL is mainly based on a clinical diagnosis [8]. Clinically, NL lesions are localized on the lower two-thirds of the legs (pretibial regions) 90% of the time [14]. Lesions typically present as one to three asymptomatic, well-circumscribed papules and nodules with active borders that slowly coalesce into plaques [13]. Plaques are typically yellowish-brown, with elevated, erythematous borders, an atrophic center, and telangiectatic vessels visible through the skin [8] (Fig. 35.1). Their texture may be similar to that of wax [12, 14]. In isolated cases, lesions may affect the upper limbs, scalp, trunk, penis, or face [6, 12]. They may ulcerate spontaneously [12]. The Koebner phenomenon may also occur [13].

Although the majority of lesions do not result in pain, as a result the associated nerve damage up to 25% can be extremely painful, especially if ulcerated [13].

Squamous cell carcinoma is a rare complication that can arise in long-standing NL lesions, presenting also without ulceration [12, 13].

Fig. 35.1 Necrobiosis lipoidica presenting as yellowish-brown plaques with well-delimitated borders and atrophic center (Photograph from the Department of Dermatology Collection, Universidade Federal de Santa Maria, Santa Maria, Brazil)

Differential diagnoses of NL include granuloma annulare, necrobiotic xanthogranuloma, morphea, sarcoidosis, and, in cases of ulceration, tuberous syphilis [9].

Complementary Examinations

The characteristic histologic features are neutrophilic necrotizing vasculitis in the early stages and amorphous degeneration and hyalinization of dermal collagen (necrobiosis) in the later stages [3].

Therapeutic Approach

It should be considered that NL is indolent, and up to 17% of lesions may resolve spontaneously. Therefore, decisions on the treatment of NL are individualized [12].

It is important to note that despite the numerous investigations carried out over the years, no treatment modalities have been shown to be completely satisfactory in treating NL [15].

Nevertheless, the primary treatment is currently the use of steroids, either topical, intralesional, or, rarely, systemic [7, 13]. Steroids should be applied to the active borders of lesions and not to atrophic areas. Steroid use in diabetic patients demands attention in order to prevent glucose dysregulation [13].

In addition to steroids, other treatments are possible, although they have only been successful in some cases or still lack scientific evidence of their effectiveness. Calcineurin inhibitors, topical retinoids, ultraviolet A phototherapy (PUVA) treatment, photodynamic therapy, and cyclosporine are some of the additional options [16]. Pentoxifylline, a potent anti-inflammatory agent with hemorrheologic effects, has been used to improve microcirculatory flow with some favorable results [17, 18].

In nondiabetic patients, baseline blood work should include a fasting blood glucose or glycosylated hemoglobin test to screen for diabetes or to assess glycemic control. If these are not diagnostic of diabetes they should be repeated on a yearly basis, as NL can be the first presentation of diabetes [12].

Lifestyle modifications, such as the avoidance of trauma, are important in minimizing the risk of NL complications [13].

Granuloma Annulare

Granuloma annulare (GA) is a common idiopathic disorder, which occurs twice as frequently in women [19]. Clinical variants include localized, generalized, subcutaneous, micropapular, nodular, perforating, and (rarely) pustular generalized perforating GA [19, 20].

Etiopathogenesis

Although the origin of this condition remains poorly understood, a marked association has been observed with certain systemic diseases, particularly diabetes and rheumatic diseases [3].

Fig. 35.2 Granuloma annulare: multiple red annular plaques organized around a slightly depressed center (Photograph courtesy of Edison Covatti, Passo Fundo, Brazil)

Clinical Presentation

The most common clinical form is localized GA, which accounts for approximately 75% of all cases [21]. It consists of pale red or violaceous papules that are firm and smooth to the touch. The lesions fuse into single or multiple annular plaques organized around a slightly depressed center [3] (Fig. 35.2). Lesions can occur anywhere on the body, but are more often found on the lateral or dorsal surfaces of the hands and feet. Symptoms are usually absent [20].

Subcutaneous or deep GA presents as a fixed nodule located on the legs, scalp, palms, or buttocks. Other less common variants include disseminated GA, characterized by a diffuse papular eruption, and a perforating form that presents as umbilicated papules with a central crust or scale and transepidermal elimination of necrobiotic connective tissue from the center [3].

Differential diagnosis for GA include other common annular skin conditions such as tinea corporis, pityriasis rosea, nummular eczema, psoriasis, or erythema migrans associated with Lyme disease. The lack of any surface changes to the skin is the key feature that distinguishes GA from these other skin conditions. Less common annular skin conditions (e.g., subacute cutaneous lupus erythematosus, erythema annulare centrifugum) have associated scaling and can be ruled out [22].

Complementary Examinations

Regardless of the clinical presentation, histologically there is dermal or subcutaneous granuloma formation with collagen necrobiosis, mucin deposition and an infiltrate consisting of histiocytes and multinucleated giant cells. Perivascular lymphocytic infiltration is also frequently observed. The histiocytes may be present in an interstitial pattern without apparent organization, or may show a palisading pattern, surrounding areas with prominent mucin [20].

Therapeutic Approach

GA treatment is frequently unnecessary because most of the lesions resolve spontaneously within 2 years of onset [3]. Nevertheless, the appearance of the lesions may require that some patients seek treatment [22].

For localized occurrences of this disease, topical corticosteroids are generally considered the first-line therapy. Depending on the site, high-potency corticosteroids with or without occlusion can be used. For nonresponsive cases, intralesional corticosteroids can be used [23]. Other options for localized disease treatment include calcineurin inhibitors, cryotherapy, or pulsed dye laser treatment. Generalized forms may be treated with one of a variety of systemic therapies, including dapsone, retinoids, niacinamide, antibiotics, antimalarials, phototherapy, or photodynamic therapy, all with only relative therapeutic success [3].

Acanthosis Nigricans

Benign acanthosis nigricans (AN) is most commonly related to endocrinopathies [24]. Obesity is the major underlying disease, often associated with hyperinsulinism, DM, and insulin resistance. Cushing's syndrome, polycystic ovaries, thyroid diseases, hirsutism, Addison's disease, and acromegaly are other endocrine disorders associated with AN [24]. All of these conditions have a significant resistance to endogenous insulin in common [25].

AN also occurs rarely as a complication of an internal malignancy, particularly of the stomach, and secondary to some medications, including nicotinic acid [25] and repeated same-site insulin injections [26].

AN is more common in dark-skinned people and is found more commonly in the adult population, although it can be observed at any age [27].

Etiopathogenesis

Elevated insulin concentrations result in the activation of IGF-1 (insulin-like growth factor 1) receptors on keratinocytes and fibroblasts, leading to epidermal cell proliferation and resulting in the clinical manifestation of hyperkeratosis and acanthosis. Other mediators may also contribute to this condition, such as EGFR (epidermal growth factor receptor) and FGFR (fibroblast growth factor receptor) [28].

Clinical Presentation

Regardless of its underlying disease presentation, AN usually follows the same pattern [25]. Presentation is characterized by symmetric, skin-colored or brownish lesions 1 mm to 1 cm in size [24, 27]. The plaques are palpable with a velvety texture and may have a flat to wart-like appearance [28].

The lesions typically form in large skin folds, particularly in the axillae, posterolateral neck, groin, and abdominal folds. Any other part of the body can also be involved, such as the nipples and phalanges [2, 24, 27] (Figs. 35.3 and 35.4). Associated skin tags are common [2].

Papillomatous growths may be encountered on the eyelids, lips, and oral mucosa, as well as on the esophageal, laryngeal, and nasal mucosa [29], and the palms (tripe palms) and dorsal surfaces of large joints [30]. These generalized forms involving mucosa, however, are more often related to malignancies [27].

Complementary Examinations

Histopathologically the lesions reveal papillomatosis, hyperkeratosis, and mild acanthosis. The dark color is due to the thickness of the keratin-containing superficial epithelium because there is no change in melanocyte number or melanin content [25].

Fig. 35.3 Papillomatous growths on the dorsal surfaces of the hands (Photograph from the Department of Dermatology Collection, Universidade Federal de Santa Maria, Santa Maria, Brazil)

Fig. 35.4 Dark velvety discoloration in acanthosis nigricans associated with skin tags (Photograph from the Department of Dermatology Collection, Universidade Federal de Santa Maria, Santa Maria, Brazil)

Therapeutic Approach

AN has better outcomes with weight reduction and optimal blood glucose control [9, 31]. The use of agents capable of increasing the differentiation and decreasing the proliferation of keratinocytes, such as topical calcipotriene or oral and topical retinoids, may also be useful. Exfoliating agents, such as urea or ammonium lactate, and depigmenting agents can also be of benefit to some patients [31].

Diabetic Bullosis

Bullosis diabeticorum (BD) is considered a rare and relatively harmless skin manifestation related to diabetic patients [32].

Etiopathogenesis

Several hypotheses have been proposed to explain the production of the bullae, such as neurotrophic disturbance, alterations in carbohydrate metabolism resulting in bullae in a manner akin to chemical vesicants, a cationic imbalance due to diabetic nephropathy, immunoglobulin-mediated vasculitis, and ischemia. Nevertheless, the exact etiopathogenesis is still unknown [33].

Clinical Presentation

Spontaneously occurring bullae without pain or any sign of inflammation generally not related to trauma or obvious physical cause are clinical features of BD. Bullae vary in size from a few millimeters to several centimeters and contain a clear, sterile fluid [33]. The main location for BD is on the distal extremities, especially the feet and lower legs, although hands and the forearms may also be involved [34] .Its evolution is self-limited and usually ceases within 2–5 weeks, without scarring. It especially occurs in patients with long-term DM [32–35].

Differential diagnoses can include epidermolysis bullosa acquisita, porphyria cutanea tarda, erythema multiforme, or drug eruption [32–35].

Complementary Examinations

Histopathologic examinations have shown inconsistent levels of skin separation, and no specific signs have been found. Therefore, skin biopsy should be used only in case of continuous eruptions suggesting a chronic skin disease [32].

Therapeutic Approach

Treatment is conservative. The blister must be kept intact in order to cover the lesion and pre-

vent secondary infection. The patient should be instructed to keep the wound clean and protected. Topical therapy is not required [35].

Scleredema Diabeticorum

Scleredema adultorum (SA) of Buschke is a fibromucinous connective tissue disorder. When associated with DM, SA is known as scleredema diabeticorum (SD) [36].

Etiopathogenesis

One proposed hypothesis for the pathogenesis of SD involves the glycosylation of collagen fibers leading to altered degradation. Another implicates hyperglycemia in stimulating fibroblasts and the synthesis of extracellular matrix components [37].

Clinical Presentation

SD is characterized clinically by diffuse, symmetric, and nonpitting induration of the skin, usually involving the neck, shoulders, trunk, face, and arms. Hands and feet are characteristically spared. Differential diagnoses of scleredema include fibrosing disorders such as scleroderma and scleromyxedema [37].

Complementary Examinations

Because of the inelasticity and induration of the thickened skin in scleredema, incisional biopsy is usually recommended to confirm the diagnosis. Histologic analysis shows a thickened dermis with increased deposition of glycosaminoglycans, mainly hyaluronic acid [37, 38]. However, diagnostic imaging may be helpful in accurately evaluating the activity of the disease in cutaneous sclerotic disorders [38].

Therapeutic Approach

There is no standard therapeutic approach for SD. Systemic corticosteroids alone or in combination with cyclophosphamide may facilitate infections and aggravate the diabetic state. The therapeutic effect of PUVA, prostaglandin E_1, methotrexate, and cyclosporine is uncertain [9]. Glucose control has not been firmly associated with improvement of the disease [37].

Kyrle's Disease

Perforating disorders are a group of unrelated pathologic abnormalities showing the common property of histopathologic transepidermal elimination, whereby the extrusion of altered dermal substances or foreign material through the epidermal channel occurs [39].

Elastosis perforans serpiginosa, reactive perforating collagenosis, perforating folliculitis, and Kyrle's disease (KD) are all classic perforating dermatoses. Clinical and histologic features of these diseases are not uniform and may resemble any of the four diseases [40].

KD is regarded as a genetically determined disease with onset occurring during adulthood, usually between the ages of 30 and 50 years and with a female-to-male ratio of up to 6:1 [41]. Chronic renal failure and/or DM usually accompany this skin disease [40].

Etiopathogenesis

In patients with KD, keratin is the predominant eliminated material. This disorder of keratinization results in the development of dyskeratotic cells at multiple points. These cells have a limited capacity for proliferation. Eventually this results in depleted cells and a consequent defect in the epidermis [42].

Clinical Presentation

KD is characterized by the eruption of asymptomatic, mildly pruritic pinhead-sized papules with silvery scales. These gradually enlarge to form reddish-brown papules and papulonodules with central keratotic cone-shaped plugs, which can be removed with a curette. The papules may be follicular or extrafollicular. Koebner's phenomenon is uncommon, although at times the lesions may

be linear [43]. The lower extremities are involved more frequently, but the upper extremities, head, and neck may also be affected [44].

Complementary Examinations

Histologically there are large keratotic and parakeratotic plugs penetrating from the epidermis through the dermis. The plugs cause inflammatory responses and a foreign-body giant cell reaction in the dermis. Mild degenerative changes in the connective tissue with no increase in the elastic tissue may also be noted. KD can remain inactive for years, with a possible clearing of lesions when the associated illness is under control [44].

Therapeutic Approach

Treatment of perforating disorders is difficult. Nevertheless, spontaneous resolution is possible [45]. Prognosis depends on the underlying disease and its response to treatment. In idiopathic cases and treatment-resistant secondary cases, topical steroids and topical and oral retinoids, along with UVB therapy, constitute the first-line therapies [46]. Narrowband UVB also appears to be an effective adjuvant phototherapeutic regimen [45].

Nonspecific Skin Conditions Associated with Diabetes

Skin Tags

Acrochordon or fibroepithelial polyps, commonly known as skin tags (STs), are one of the most common benign skin conditions [47].

Acrochordon is regarded as a sign of impaired glucose tolerance, DM, and increased cardiovascular (atherogenic lipid profile) risk [48]. STs may also play a role in the early diagnosis of metabolic syndrome [47].

Etiopathogenesis

In hyperinsulinemia, insulin is able to activate IGF-1 receptors present on fibroblast and keratinocyte surfaces in a similar way to what occurs in the pathogenesis of AN [49]. Two studies have found the presence of human papillomavirus DNA in STs, at frequencies of 48% [50] and 88% [51].

Clinical Presentation

STs are consisting of skin projecting from the surrounding skin, usually occurring on the eyelids, neck, and axillae [47].

Complementary Examinations

There are no complementary examinations that need to be performed to investigate STs.

Therapeutic Approach

Because they are generally of only cosmetic concern, treatment of STs is not required, and cutting the pedicles of the tags can be performed with microscissors and microforceps [52]. Cryotherapy and electrodesiccation can also be used [53].

Patients with STs also need suitable interventions, such as weight reduction, smoking cessation, and changes in dietary habits [47].

Rubeosis Faciei

Rubeosis, also named rubeosis faciei and rubeosis faciei diabeticorum [54], is a relatively common skin manifestation associated with diabetes that may go unnoticed by patients and physicians [7].

Etiopathogenesis

Hyperglycemia could lead to sluggish microcirculation, which becomes clinically evident from facial venous dilatation; its presence should lead to the evaluation of the patients for other more important microangiopathies, such as retinopathy [7].

Clinical Presentation

Rubeosis presents as a flushing that can be observed more frequently in association with type 1 DM (21–59%). Rubeosis is more prominent in fair-skinned people and usually involves the face, neck, hands, and feet [1].

Complementary Examinations

Rubeosis faciei is a clinical diagnosis and does not demand complementary examinations.

Therapeutic Approach

No treatment is needed, although strict glycemic control can improve the appearance and prevent

complications related to microangiopathy in other organ systems [7, 54].

Yellow Skin

Yellow pigmentation of the skin (xanthoderma) may be associated with carotenemia, hypothyroidism, liver disease, and renal disease. The frequency of this phenomenon in diabetic patients is unknown, and the relationship between skin color and blood carotenoid level is controversial [55].

Etiopathogenesis

Not much is known about the relationship of diabetes and yellow skin. Traditionally yellow skin is considered to be related to carotenemia, whereby there are increased β-carotene levels in the blood, but it may also be associated with end products of advanced glycation [56].

Clinical Presentation

Carotenemia is a clinical condition characterized by yellow pigmentation of the skin (xanthoderma) [55]. Carotene deposits are usually most notable in areas with a thick stratum corneum, such as the nasolabial folds, palms, and soles, as opposed to areas such as the conjunctivae and mucosa [57].

Complementary Examinations

Tests for carotene levels can be performed but are generally unnecessary to evaluate yellow skin in diabetic patients.

Therapeutic Approach

No treatment is required, although adjustments to the glycemic level may result in an improvement in the yellow discoloration of the patient's palms and soles.

Xerosis

Rough skin or xerosis, commonly known as dry skin, results from a defect in the stratum corneum. This condition is negatively influenced by winter climatic conditions. DM, as well as other endocrine and metabolic disturbances, is also involved in this condition [58].

Etiopathogenesis

Xerosis is considered to be related to an autonomic peripheral C-fiber neuropathy, and it has been speculated that other factors, such as stratum corneum adhesion and accelerated aging of the skin, may be involved in the development of xerotic skin changes in diabetic patients [59].

Clinical Presentation

Dry skin can affect the extremities, trunk, or even the whole body. Cracking and fissuring of the epidermis can be visible.

Complementary Examinations

No complementary examinations need to be performed to xerosis related to DM.

Therapeutic Approach

Xerosis can be improved to various degrees by emollients, humectants, hydrating agents, and squamolytic agents [58].

Doctors should educate patients about the importance of skin hygiene, including applying fragrance-free creams or lotions within 3 min of bathing to trap moisture within the skin [7].

Diabetic Pruritus

Pruritus is difficult to characterize and define. Various indirect definitions have been proposed that include a sensation which provokes the desire to scratch or an uneasy sensation of irritation in the skin [60].

Itching in people with diabetes frequently can be secondary to many of the skin conditions already mentioned. Nevertheless, chronic pruritus with no primary skin condition is thought to affect a considerable percentage of diabetic patients, with some studies suggesting it affects 3–49% of all diabetics [9].

A large-scale survey of 2,656 diabetic outpatients and 499 nondiabetic subjects was performed between November 2006 and August 2007. The prevalence of truncal pruritus of unknown origin in diabetic subjects was significantly higher than that in nondiabetic subjects [61].

Pruritus is a risk factor for self-injuring behavior in sensory polyneuropathies because itching

often induces scratching that can lead to clinically significant tissue damage [62].

Etiopathogenesis

Itches originating in the skin are considered pruritoceptive and can be induced by a variety of stimuli, including mechanical, chemical, thermal, and electrical stimulation [63].

Diabetic polyneuropathy (small fiber neuropathy with damage to myelinated Aδ and nonmyelinated C fibers) and xeroderma (aggravated by age and hypohidrosis in diabetic autonomic neuropathy), as well as certain drugs (glimepiride, metformin, and tolbutamide), have all been implicated in the pathogenesis of diabetic pruritus [9].

Clinical Presentation

Generalized pruritus is considered to be a sign of diabetes. Neuropathic pruritus may cause generalized truncal pruritus and localized itching, particularly in the genital areas of diabetic patients [64].

Complementary Examinations

Skin biopsies are nonspecific and may only help if there is an underlying skin disease suspected as the cause of the symptoms.

One study showed a positive association between postprandial blood glucose and generalized pruritus, suggesting that better control of postprandial glucose might be beneficial to relieve generalized pruritus in diabetic patients [65].

Therapeutic Approach

Symptomatic therapies may include high-dose antihistamines and pain-modulating drugs, such as gabapentin, pregabalin, or antidepressants. Therapy with emollients containing urea and in combination with substances that mitigate pruritus is essential [9].

Psoriasis

Psoriasis is a chronic inflammatory disease associated with several comorbidities. A few decades ago, it was considered to be a disease exclusive to the skin, but today it is considered a multisystem disease. It is believed that 73% of psoriasis patients have at least one comorbidity [66]. There

are reports of a significant association between DM and psoriasis in a large series of patients with psoriasis [48].

It has been suggested that psoriasis is an independent risk factor for the development of type 2 DM, whereby the severity of psoriasis correlates with the diabetic risk [67].

Etiopathogenesis

Immune-mediated inflammatory processes, metabolic biomarkers, and environmental factors could be the potential links between psoriasis and diabetes [68].

There is probably an association between psoriasis and diabetes that is related the actions of T-helper 1 cytokines, which can promote insulin resistance and metabolic dysregulation (i.e., metabolic syndrome) and can promote inflammatory cytokines known to drive psoriasis [67].

Clinical Presentation

Chronic plaque psoriasis (psoriasis vulgaris) is the most common form of the disease and accounts for approximately 90% of the cases. Typical psoriasis lesions are monomorphic, sharply demarcated, erythematous plaques covered by silvery lamellar scales. Extensor surfaces of the forearms and shins, periumbilical, perianal, and retroauricular regions and the scalp are the most common sites for these lesions [69].

Complementary Examinations

Cutaneous psoriasis is a clinical diagnosis, and skin biopsy is rarely used. There are three main histologic features of these lesions: epidermal hyperplasia; dilated, prominent blood vessels in the dermis; and an inflammatory infiltration of leukocytes, predominantly into the dermis [70].

Despite recent advances in the systemic treatment of psoriasis, topical agents represent the primary treatment for a majority of patients with mild to moderate psoriasis, as well as for some with more severe cases of this disease [71].

Therapeutic Approach

Topical therapies such as glucocorticosteroids, vitamin D derivatives, or combinations of both are usually sufficient to manage mild cases of this

disease. Topical calcineurin inhibitors are used at difficult-to-treat sites, such as the intertriginous areas or the face. A combination of phototherapy and systemic therapy is needed for patients with moderate to severe psoriasis. Established systemic drugs for the treatment of psoriasis include methotrexate, cyclosporine, acitretin, and, in some countries, fumaric acid esters. Biologics have also been developed and approved for the treatment of psoriasis over the past few years [69].

Vitiligo

Vitiligo, an acquired pigmentary disorder of unknown origin, is the most frequent cause of depigmentation worldwide, with an estimated prevalence of 1% [72]. It is well known that vitiligo is associated with other autoimmune disorders, such as thyroid dysfunction, Addison's disease, insulin-dependent DM, and alopecia areata, showing that vitiligo shares a common genetic etiologic link with these autoimmune disorders. Insulin-dependent DM is found in 1–7% of patients with vitiligo, and conversely, 4.8% of all diabetic patients were found to have vitiligo [73].

Etiopathogenesis

The leading theory of vitiligo's etiology involves an autoimmune cause linked to specific genetic mutations. Although the role of antimelanocyte antibodies in vitiligo is still not well known, high levels of circulating autoantibodies have been found in approximately 10% of patients, especially against tyrosinases 1 and 2 [74].

Clinical Presentation

The most typical skin lesion is an asymptomatic, whitish macule or patch, with regular borders and sharp margins surrounded by normal or hyperpigmented skin [74].

Complementary Examinations

Histologic examination and immunohistochemical studies with a large panel of antibodies generally show an absence of melanocytes in lesional skin, although sometimes a limited number of melanocytes can be observed [72].

Therapeutic Approach

Topical therapy and narrowband UVB are the safest and most effective treatment options in most cases of vitiligo. Topical corticosteroids are still the primary treatment for localized forms of vitiligo because of their wide availability, low cost, and efficacy. Systemic therapy can be attempted in cases of disseminated vitiligo lesions, and in these cases steroids still remain the principal therapy. Surgical therapy could be useful in patients for whom medical therapy has failed [74].

Lichen Planus

Lichen planus (LP) is an uncommon disorder affecting <1% of the general population [7]. Some studies have shown a significant association between LP and increased disturbances of glucose metabolism including DM, glucose intolerance, and insulin resistance [75, 76].

Etiopathogenesis

LP is caused by an autoimmune process mediated by different types of cells and triggered by antigen alterations on the cell surface of the basal layer of the epithelium. In addition, epidermal cells have shown abnormalities in their enzymatic activity, as well as defective carbohydrate regulation in cases of LP, which might be connected with hormones essential for metabolic processes [75].

Clinical Presentation

LP presents as grouped, symmetric, erythematous to violaceous, flat-topped, polygonal papules distributed mainly in the flexural aspects of the arms and legs, and can rarely appear on the trunk. The Koebner phenomenon is common, and the pruritus associated is intense and heals with postinflammatory hyperpigmentation [7].

Complementary Examinations

Histologic examination of the skin or mucosal biopsies is useful to confirm the diagnosis in atypical cases, as well as to avoid inappropriate treatment in cases of severe disease [77].

Therapeutic Approach

Because the cutaneous form of LP may resolve spontaneously, the goals of therapy are to shorten the time between the onset and resolution of the lesions and to reduce itching. Topical glucocorticoids are the first-line treatment. When topical treatments are ineffective, oral glucocorticoid therapy is sometimes used. Other options are phototherapy and oral aromatic retinoids [77].

Skin Complications Associated with Diabetes Mellitus

Diabetic Foot Syndrome

Diabetic foot syndrome is defined as a group of clinical manifestations associated with neurologic abnormalities and various degrees of peripheral vascular disease in the lower limbs of diabetic patients. Ulceration, infection, and/or destruction of the deep tissues can occur [78].

Approximately 30% of diabetics will suffer from metabolic polyneuropathy, which is characterized by symmetric, distal, chronic, insidious onset, and somatic (sensorimotor) and autonomic dysfunction. An inability to detect temperature changes, excessive pressure, and continued traumas develop. Atrophy and weakening of the intrinsic muscles of the foot lead to deformities and abnormal biomechanical loading of the foot. Autonomic neuropathy results in anhidrosis, causing dry skin, fissures, and callused areas with secondary ulceration [79, 80].

The other component of diabetic foot syndrome involves vascular disease. Ischemia reduces the supply of oxygen, nutrients, and soluble mediators that are involved in the skin repair process. Furthermore, hyperglycemia-induced nerve dysfunction leads to the dysregulation of nerve microvasculature and consequent neuropathy [81].

Plantar Ulcers

Foot ulcerations are one of the most serious and disabling complications of DM and are the most common cause of nontraumatic foot amputation [82]. The prevalence of ulcers in the diabetic population ranges from 4% to 25% [81, 83]. Each patient with DM requires a comprehensive foot examination annually to identify risk factors for neuropathy and any evidence of neuropathy or ulceration [81].

Etiopathogenesis

Foot ulcerations are the result of neurologic abnormalities and various degrees of peripheral vascular disease. Both factors work in predisposing patients to ulcers and also making it difficult for ulcers to heal.

Clinical Presentation

The most common locations for foot ulcers are in the projections of the first, second, or fifth metatarsal bone, but may occur in other locations such as the heel and outer edge of the foot or toes. They are painless lesions because surface and depth sensitivity are impaired. Therefore, patients may continually traumatize the ulcerated location, making healing difficult [14].

Measurement of cutaneous pressure perception with the use of Semmes–Weinstein monofilaments is a validated screening test for the potential for neuropathy and ulcers. The loss of pressure sensation at four sites, as detected by the unperceived buckling of a 10-g monofilament, is highly predictive of subsequent ulceration. The four sites include the first, third, and fifth metatarsal heads, and the plantar surface of distal hallux. In addition, vibration testing with a 128-Hz tuning fork applied at a bony prominence is a useful test for peripheral neuropathy. The ankle jerk and patellar reflexes are also examined [81].

In purely neuropathic ulcers the foot is typically warm, pulses are palpable, and there is hypohidrosis. In contrast, in neuroischemic ulcers the foot is cold, pedal pulses are not palpable, and there is atrophy of the subcutaneous muscles and skin appendages [9].

Complementary Examinations

Radiography and other imaging modalities can help in detecting structural changes related to diabetic foot syndrome. Magnetic resonance imaging has high sensitivity and specificity for cases where infection with osteomyelitis is suspected [84].

Therapeutic Approach

The management of a diabetic foot ulcer has better outcomes when a multidisciplinary team is involved [81]. A combination of prevention and infection control, pressure removal thorough relief shoes or devices such as casts or boots, debridement, and dressings are used in combination [78].

Considering that abnormal glucose levels affect the nature of infection and cellular immunity, optimizing glucose control was previously highlighted as crucial for wound healing. Nevertheless, evidence from a recent study was unable to conclude whether intensive glycemic control had a positive or detrimental effect on the treatment of foot ulcers in people with diabetes when compared with conventional glycemic control [85].

The importance of avoiding walking barefoot and potential trauma should be impressed on the patient. Appropriate footwear is essential. The removal of mechanical pressure from a neuropathic foot ulcer is central to the healing of the ulcer. Resting the foot and the use of a nonremovable, total-contact cast is associated with more rapid healing rates [81]. The use of orthopedic innersoles, in accordance with various "offloading" foot techniques using various material features, has also led to good results [14].

The use of moist dressings on clean granulating wounds improves the wound environment. They provide protection against further infection, maintain moisture balance and pH, absorb fibrinous fluids, and reduce local pain. The choice of dressing is further guided by patient requirements and treatment costs [81].

Debridement is the process whereby all materials incompatible with healing are removed from a wound. Several methods are currently used for debridement, including surgery, conventional dressings, larvae, enzyme preparations, polysaccharide beads, and hydrogels. The choice of method should be based on the available expertise, patient preferences, clinical context, and costs [86].

If there are any signs of infection, further investigation should be performed and then followed by the administration of systemic antibiotics according to antibiogram results [9, 81].

There is low- to moderate-quality evidence that suggests a beneficial effect of hyperbaric oxygen therapy when used as an adjunct to standard treatments for diabetic foot ulcers [87].

Charcot Foot

Although Charcot foot does not primarily affect the skin, dermatologists should be familiar with this disorder, as its acute form may imitate erysipelas/cellulitis, deep vein thrombosis, or an acute gout attack [9, 88].

Charcot neuroarthropathy (CN) is an uncommon complication in diabetes that is characterized by severe deformity of the foot and/or the ankle that when not detected early will result in secondary ulceration, infection, and ultimately amputation [89].

Although Charcot foot occurs most often in patients with diabetic neuropathy, other predisposing conditions include alcoholic neuropathy, sensory loss caused by cerebral palsy or leprosy, and a congenital insensitivity to pain [90].

The prevalence of CN in diabetic patients ranges from 0.08% to 8.5%, and most patients who develop CN have had a known duration of diabetes of more than 10 years [84, 89].

Etiopathogenesis

The interaction of several component factors (diabetes, sensorimotor neuropathy, autonomic neuropathy, trauma, and metabolic abnormalities of bone tissue) results in an acute localized inflammatory condition that can lead to varying degrees and patterns of bone destruction, subluxation, dislocation, and deformity [84].

Clinical Presentation

Although Charcot foot is more common unilaterally, it can involve both extremities in up to 39% of cases [89]. The most common presentation is a neuropathic patient who sustains an unperceived injury, continues to walk until a severe inflammatory process leads to osteopenia, distention of the joint, and end-stage foot and/or ankle dislocation [89].

Musculoskeletal deformities in cases of Charcot foot can be very slight or grossly evident, most often owing to the chronicity of the

problem and the anatomic site involved. The classic rocker-bottom foot, with or without plantar ulceration, represents a severe chronic deformity and is typical for this condition [84].

All physicians treating diabetic patients should be vigilant in recognizing the early signs of an acute process such as unexplained pain, warmth, edema, or pathologic fractures in a neuropathic foot [84].

The patient often has no recollection of an inciting event or reports only a minor injury. Vital signs are typically stable. The patient may have already been treated for recurrent cellulitis. The edematous limb is often without any open wounds and has increased warmth and erythema, which resolves with the elevation of the foot [88]. If the swelling and rubor persist during this technique, an infectious process is likely to be present.

Complementary Examinations
In the acute stage of CN, venous duplex ultrasonography will likely show negative results for deep vein thrombosis [88].

The erythrocyte sedimentation rate, C-reactive protein values, and white blood cell count are also usually found to be normal [91].

Results from radiography and other imaging modalities may detect subtle changes consistent with active CN or may be normal, emphasizing the importance of early utilization of advanced imaging [84, 88].

Magnetic resonance imaging allows for the detection of subtle changes in the early stages of active CN. It has high sensitivity and specificity for osteomyelitis and has become the test of choice for the evaluation of foot complications in diabetic patients [84].

Therapeutic Approach
The modern approach to treating CN is to diagnose it as early as possible and to institute timely off-loading to avoid adverse outcomes [91].

Total contact casting is well recognized as the gold-standard treatment for CN in general, although it has not become a standard treatment in many diabetic foot clinics because of concerns about complications [91]. Immobilization can be achieved with either a nonremovable or removable cast for an average duration of 14 weeks [88].

Surgical treatment is indicated for chronic recurrent ulcerations and joint instability when patients present with unstable or displaced fracture dislocations. Treatment outcomes and complication rates vary between centers [91].

Cutaneous Infections
Patients with DM are more prone to infections than healthy individuals [6, 9]. Moreover, diabetics exhibit a five-fold increase in complication risks compared with nondiabetics in cases of skin and soft tissue infections [9]. Incidences of infection correlate with mean blood glucose levels [6].

The disturbed skin barrier in diabetic patients and diabetes-induced vasculopathies, together with neuropathies, have been implicated in an increased vulnerability to infections. Recurrent bacterial infections, such as impetigo contagiosa, abscesses, erythrasma, folliculitis, erysipelas, or severe fungal infections, should alert physicians to screen for DM [8].

Treatment options for bacterial infections include the use of local antiseptics or antibiotic agents and, in cases of progressive soft tissue involvement or systemic signs of infection, the use of systemic antibiotics [6, 9].

Patients with diabetes are believed to be particularly susceptible to *Candida* infection because increased glucose concentrations permit the organism to thrive [9]. Thrush, angular cheilitis, candidal balanoposthitis, vulvovaginitis, and paronychia, as well as intertriginous candidiasis, are all common among diabetic patients. In contrast, the increased prevalence of dermatophytosis in diabetic patients is still a matter of controversy [8, 9].

Fungal infection of the nails is also common in diabetes [6]. Up to one-third of diabetics may have onychomycosis, which is a significant predictor of the development of foot ulcers in diabetes [92]. Therefore, treatment must not be neglected in these cases.

Furthermore, foot infections remain the most frequent diabetic complication requiring hospitalization and the most common precipitating event leading to lower extremity amputation [91].

Usually a consequence of an ulceration, the presence of a foot infection is generally indicated by the presence of systemic signs of infection or purulent secretions or by two or more local symptoms (redness, warmth, induration, pain, or tenderness). It is also important to note that local signs of infection can be diminished because of peripheral arterial disease and neuropathy. Osteomyelitis may affect up to two-thirds of patient with diabetic ulcers and may occur without pain [81].

Nasal and eyelid inflammatory lesions in diabetic patients deserve special attention. The possibility of mucormycosis, a rapidly progressive and potentially lethal infection caused by fungus primarily of the genera *Rhizopus* or *Mucor*, must not be ignored. Cutaneous mucormycosis is usually due to skin inoculation or local trauma introducing spores into the dermal layer, where vascular invasion by hyphae can cause infarction and necrosis of tissues. Rhino-orbital-cerebral and pulmonary infections are the most common presentations [93].

Diabetic Hand Syndrome

The term "diabetic hand" is used to characterize complications of DM that occur in the hands. Although the term "diabetic hand" has no precise definition in the literature, Papanas and Maltezos propose defining it as a syndrome of musculoskeletal manifestations of the hand (mainly limited joint mobility, Dupuytren's contracture, and trigger finger) in diabetic patients that is usually associated with long-standing diabetes, suboptimal glycemic control, and microvascular complications. Neuropathic hand ulcers and diabetic hand infections are also cited by the authors as part of the definition of "diabetic hand" [94].

Limited Joint Mobility Syndrome

Limited joint mobility syndrome (LJMS), diabetic sclerosis, the pseudosclerodermatous hand of the diabetic, and diabetic stiff hand are some of the diagnostic terms used in the medical literature referring to diabetic cheiroarthropathy (DCA) [95].

Increased nonenzymatic collagen glycosylation due to chronic hyperglycemia may lead to increased crosslinking between collagen molecules, thereby conferring an increased resistance to collagenases, manifesting clinically as stiffness [94].

Diagnosis is based on the following clinical features: progression of the painless stiffness of hands and fingers (prayer sign), fixed flexion contractures of the small joints of the hands and feet, impairment of fine motion, and impaired grip strength in the hands. As the syndrome progresses, it can also affect other joints [96].

It is important to diagnose LJMS because its presence is associated with the micro- and macrovascular complications of diabetes.

Because of the lack of curative treatment options, the suggested method to prevent or decelerate the development of LJMS is to improve or maintain good glycemic control. Daily joint-stretching exercises aimed at preventing or delaying the progression of joint stiffness may reduce the risk of inadvertent falls and will help maintain quality of life [96].

Dupuytren's Contracture

Dupuytren's contracture (DC) is characterized by palmar fascia thickening, palmar and digital nodules, skin thickening and adherence, pretendinous band formation, and digital flexion contracture. DC affects 16–32% of diabetic patients and is more common among the elderly and those who have had DM for longer periods. It mainly affects the third and fourth fingers, rather than the fourth and fifth fingers, as typically occurs in cases associated with other etiologies [97]. Dupuytren's contracture has been treated with intralesional infiltration of corticosteroids, surgery, and physical therapy [97].

Trigger Finger

Stenosing flexor tenosynovitis typically presents as fingers locked in flexion, extension, or both, more commonly involving the thumb, third finger, and/or fourth finger [97].

The treatment for stenosing flexor tenosynovitis includes a change in activities, the use of nonsteroidal anti-inflammatories, splinting, infiltrations, and, in more severe cases, surgery [97].

Tropical Diabetic Hand Syndrome and Hand Infections

Tropical diabetic hand syndrome is a complication affecting patients with DM that is much less recognized that foot infections.

The syndrome encompasses manifestations that range from a localized cellulitis with variable swelling and ulceration of the hands to progressive, fulminant hand sepsis and gangrene affecting the entire limb [98].

Typically, patients have type 2 DM, are female, present in their fifth to sixth decade of life, and have poor metabolic control. Antecedent trauma (mild abrasion, laceration, insect bites) is often reported [94].

While tropical diabetic hand syndrome is essentially confined to the tropics, hand infections may also occur in the general diabetic population of the Western world. *Staphylococcus aureus* is the most common bacterial isolate, while infections by *Streptococcus*, *Klebsiella, Enterobacter*, *Proteus*, *Escherichia coli*, and various anaerobes may also be found [94].

Early diagnosis and treatment may lead to adequate recovery. Prognosis improves when appropriate blood glucose and insulin control, antimicrobial therapy, drainage, and debridement are performed promptly after diagnosis [99].

Peripheral Neuropathy and Ulceration

Although diabetic foot problems related to peripheral neuropathy are well reported in the literature, we tend to forget the possible involvement of the hands. However, sensory impairment of the hands may occur in patients with severe neuropathy [100].

Screening for hand neuropathies is not a normal practice in most clinics unless patients are symptomatic (e.g., hand numbness or tingling). Such hand symptoms are, however, uncommon, and patients are unaware of neural dysfunction. Marked hand symptoms also seem to be more related to carpal tunnel syndrome than to neuropathy [100].

Hand examinations should not be neglected in patients with severe neuropathy in the feet and/or foot burns. Such patients need to be warned about the danger of hand burns [94].

Education on hand care should be given more attention, particularly in patients with lower extremity neuropathy. Patients in certain occupations (e.g., those that involve handling of hot materials or vibrating machinery) may be at particular risk, and the necessary precautions must be assured in their work environment [94].

Conclusion

DM and insulin resistance are related to a wide range of skin manifestations. Therefore, doctors should be aware of these skin conditions to best assist patients with this metabolic disorder.

Glossary

Acanthosis Hyperplasia of the squamous epithelium.

Acanthosis Nigricans Dark pigmentation with a velvety texture in large skin folds.

Acrochordon Benign pedunculated skin growths usually occurring on the eyelids, neck, and axillae.

Charcot foot Complication in diabetes that is characterized by severe deformity of the foot and/or the ankle that when not detected early may result in secondary ulceration, infection, and amputation.

Diabetic dermopathy Also known as "shin spots," a specific skin condition associated with diabetes mellitus.

Flushing Redness of the skin together with a sensation of local warmth or burning.

Koebner reaction A phenomenon where new lesions appear along a site of trauma or irritation of the skin can. Examples: lichen planus, psoriasis.

lichen planus Inflammatory chronic skin condition of flat-topped erythematous to violaceous papules caused by an autoimmune process,

Macule A change in the color of the skin that is neither raised nor depressed, up to 1 cm in diameter.

Melanocytes Pigment cells responsible for producing melanin. In the human skin they are

found in the basal layer of the epidermis and hair follicles.

Necrobiosis   Gradual degeneration and death of a cell.

Necrobiosis lipoidica   Skin disease marked by one or more tender yellowish brown patches often associated with diabetes mellitus.

Psoriasis   An autoimmune skin condition that changes the life cycle of skin cells. The majority of patients presents lesions as clearly defined red and scaly plaques.

Scleredema   A dermatologic disorder characterized by hardening and thickening of the skin. When associated with diabetes mellitus is called "scleredema diabeticorum."

Vitiligo   An acquired pigmentary disorder of unknown origin characterized by portions of the skin losing their pigment.

Xanthoderma   Yellow pigmentation of the skin.

Xerosis   Commonly known as "dry skin," results from a defect in the stratum corneum.

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Diseases of Thyroid

36

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Key Points Summary
- Hyperthyroidism and hypothyroidism are disorders with important interaction with the skin
- Iodine intake levels below and above the recommended level are associated with the occurrence of thyroid disorders

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- Thyroid hormone deficiency causes thickening, hyperkeratosis, diffuse loss of scalp hair, and nail atrophy
- Generalized myxedema is a severe disease that may occur in hypothyroidism, when mucin is deposited in the skin and other organs resulting in a series of dermatologic and systemic outcomes
- Pretibial myxedema is less frequent, being present in only 5% of cases of Graves' disease. About 90% of pretibial myxedema patients have hyperthyroidism
- Thyroid acropachy is a rare manifestation of thyroid autoimmune disease and can display finger or toe clubbing and edema
- Thyroglossal cyst and cutaneous metastases of thyroid cancer are other diseases associated with the thyroid gland

Epidemiology

Thyroid diseases are considered very frequent diseases. Estimates report that hyperthyroidism affects about 2% of the general population, with a 15% increase among the elderly, occurring predominantly in females and in iodine ingestion–deficient regions [1]. Congenital hypothyroidism (cretinism) has an incidence of 1 case per 4000 births; 19% are

sporadic and 5% are genetic. Hashimoto's thyroiditis mainly affects women between the ages of 30 and 50 years, with a female-to-male ratio of 7:1. Postpartum thyroiditis occurs in about 8–10% of women [2]. Hyperthyroidism has a lower prevalence (2% in women and 0.2% in men (English data)) [1]. Regarding Graves' ophthalmopathy in the general population, there are incidence reports of 16 women and 3 men in every 100,000 population per year [3].

Among many dermatologic manifestations, pruritus sine materia seems to be a significant manifestation of thyroidopathies (Artantas et al. [4] report a pruritus prevalence of 2.7% in patients with thyroid disturbances).

The Thyroid and the Environment

Iodine (as iodide) is widely but unevenly distributed in the earth's environment. Most iodide is found in the oceans (about 50 μg/L), and iodide ions in the seawater oxidize to form elemental iodine, which is volatile and evaporates into the atmosphere and returns to the soil through rain, completing the cycle. However, the cycle of iodine in many regions is slow and incomplete, and soils and groundwater become deficient in iodine. Crops grown in these soils will contain low iodine concentrations, and humans and animals consuming food grown in these soils become deficient in iodine [2].

Iodine consists of 65% and 59% of the weights of thyroxine (T4) and tri-iodothyronine (T3), respectively. Thyroid function is crucial for the metabolism of almost all tissues and for the development of the central nervous system in fetuses and children.

Iodine deficiency is the result of insufficient dietary iodine intake, and the physiologic consequence is abnormal thyroid function, hypothyroidism, and goiter [3]. In nearly all regions affected by iodine deficiency, the most effective way to control iodine deficiency is through salt iodization. The World Health Organization / United Nations Children's Fund / International Council for the Control of the Iodine Deficiency Disorders (WHO/UNICEF/ICCIDD) recommends that iodine be added at a concentration of 20–40 mg iodine/kg of salt, depending on local salt intake [3].

A sudden increase in iodine intake in an iodine-deficient population may induce thyroid autoimmunity. It is well established that individual patients with autoimmune thyroiditis may develop hypothyroidism when exposed to excess iodine. Considering the very frequent occurrence of thyroid autoimmunity in the population, it would be expected that a high iodine intake would be associated with a high frequency of subclinical (with elevated serum thyroid-stimulating hormone (TSH) but a free T4 estimate within the reference range) and overt (elevated TSH and a low estimate of free T4) hypothyroidism, and this has indeed been convincingly demonstrated [4, 5].

Four methods are generally recommended to assess iodine intake: urinary iodine concentration, goiter rate, serum TSH, and serum thyroglobulin [4]. The spectrum of disorders that somehow depend on the iodine intake level of the population can be based on the median or range of urinary iodine concentrations, or both. High intake of iodine results in a urinary iodine concentration of 100–200 μg/L. Below these concentrations (50–25 μg/L) insufficient iodine intake occurs, resulting in diseases ranging from cretinism and low IQ to goiter with hypothyroidism or hyperthyroidism. High urinary concentrations of iodine (>300 μg/L) may result in early Graves' disease (GD) [2].

Thus, the thyroid gland contains an advanced set of processes that may enhance or block the use of iodine for thyroid hormone production. Because the processes activated with low and high iodine intakes are different, the type of disease that dominates thyroid pathology in populations may be different depending on the level of iodine intake.

Skin Manifestations of Hyperthyroidism

Hyperthyroidism, or excess circulating thyroid hormone, results from a disturbance in any portion of the hypothalamic-pituitary-thyroid axis. In normal subjects, TSH is made by the pituitary gland and stimulates the thyroid gland to generate and secrete T4 (thyroxine) and T3

(triiodothyronine). In the periphery, T4 is converted into T3 by enzymes mainly in the liver and kidney. T3 (and to some extent T4) then binds to specific nuclear receptors in the tissues (e.g., heart, brain, muscle, and perhaps skin) and mediates the thyroid hormone action [6].

Furthermore, the amount of T4 and T3 secreted by the thyroid gland is regulated by a negative feedback system of the pituitary gland. Specifically, when the body recognizes it has excess thyroid hormone levels, T3 (and T4) binds to the TSH gene regulatory elements in the pituitary gland and inhibits TSH production [7].

Hyperthyroidism is more commonly seen in women than in men (5:1 ratio). The most characteristic (although rare) skin finding in GD is pretibial myxedema, although other more common cutaneous manifestations of hyperthyroidism include warm, flushed, moist skin, with generalized increased sweating [7, 8].

The skin changes, and the hair may become thin and soft; loss of scalp, eyebrow, axillary, pubic, or body hair is common. Hair loss without scarring (alopecia areata) is most often associated with autoimmune disease (GD) [9].

Up to 25% of patients with GD have clinically obvious Graves' ophthalmopathy at the time of the diagnosis of hyperthyroidism [9].

The nails may become soft and friable, and separation of the distal nail plate from the nail bed may occur, producing Plummer's nails [10].

A definitive treatment of hyperthyroidism varies depending on the etiology of the disorder, but usually involves rendering the patient euthyroid with antithyroid drugs (i.e., methimazole or propylthiouracil).

These antithyroid agents can cause pruritic erythematous skin rash, hepatotoxicity, arthralgias, or bone marrow suppression [11].

The implementation of a definitive therapy may include long-term antithyroid agents, radioactive iodine therapy, or thyroidectomy. It requires radioactive iodine from 2 to 3 months to cause hypothyroidism [6].

The skin manifestations associated with hyperthyroidism are classically cleared with treatment of the underlying cause of the hyperthyroidism state as described below [10].

Etiopathogenesis

GD results from stimulation of the TSH receptor through receptor-binding antibodies. Thus, the usual negative report promoted by the T3 and T4 levels of TSH production by the hypophysis is interrupted. The outcome of this abnormal mechanism is excessive T3 and T4 in the peripheral circulation, which entails the clinical manifestations of hyperthyroidism. High levels of T3 and T4 promote the usually seen clinical symptoms of the disease, such as nervousness, anxiety, weight loss, heat intolerance, fatigue, muscle weakness, and palpitations [12].

The dermatologic and ophthalmologic manifestations specific to the thyroid diseases result from the autoimmune effects of antibodies of the TSH, rather than being related to the circulating thyroid hormone levels. In the dermatologic diseases nonspecific to the cutaneous thyroid, alterations are directly related to the circulating levels of T3 and T4 [12].

Clinical Presentation

Dermatologic manifestations of hyperthyroidism vary. The skin is warm, soft, humid, blushed, and tender, and an association with cutaneous pruritus is frequent. Hyperhidrosis may be noticed mainly in the hand palms and feet soles [4].

The hair may become thinner and soft, and hair loss in the scalp, eyebrows, axillae, pubic area, or throughout the body is common.

Complementary Examinations

The blood dosage of free TSH, T3, and T4 levels added to the clinical signs and symptoms of hyperthyroidism seal the diagnosis.

Therapeutic Approach

Treatment includes normalizing the thyroid function, either through medication or the thyroid function ablation [12, 13].

Special Considerations

Graves Ophthalmopathy

Thyroid ophthalmopathy is an autoimmune orbit disease closely associated with GD, although both conditions may exist separately [13].

Around 20–25% of GD patients have ophthalmopathy [14]. The ophthalmopathy develops before the hyperthyroidism presentation in around 20% of patients; concomitantly in 40%; and in 40% of the cases 6 months after the diagnosis [15]. It is worth bearing in mind that the ocular disease may become evident after hyperthyroidism treatment, usually in patients treated with radioiodine [16].

Etiopathogenesis

The most often accepted theory to explain the association between thyroid ophthalmopathy and autoimmune thyroid disease is a possible cross-relationship of sensitized T lymphocytes and/or antibodies against the thyroid and the orbit common antigens [17].

The volume of retro-orbital connective and adipose tissue and the volume of extraocular muscles are increased by cell proliferation, inflammation, and glycosaminoglycan accumulation, mainly hyaluronic acid. Glycosaminoglycan secretion by the fibroblasts is activated by the T-cell cytokines (tumor necrosis factor, interferon-γ), thus showing that T- and B-cell activation is important for the immunopathogenesis of Graves' ophthalmopathy. Glycosaminoglycan accumulation brings about changes in the osmotic pressure which lead to liquid accumulation, muscular edema, and increased pressure inside the orbit. These changes, with the addition of retro-orbital adipogenesis, move the eyeball outside, possibly also interfering in the function of the extraocular muscles and the orbit's venous drainage [12, 13].

Clinical Presentation

The extraocular muscles are the main impaired targets and show increased volume, and together with other important clinical signs determined by inflammatory changes and/or vascular congestion include upper and lower eyelid retraction, conjunctival hyperemia, and preorbital edema [17, 18], as well as sequelae of extraocular muscle hypertrophy translated into visual loss that results from corneal ulceration, secondary to proptosis and optical neuropathy by compression of the optic nerve [17, 19]. Exophthalmos is almost always bilateral and symmetric. The lower rectus muscle is the most often involved muscle followed by the medial rectus, the upper rectus, and the lateral rectus muscles (Figs. 36.1 and 36.2).

Complementary Examinations

The diagnosis is clinical, and imaging methods are indicated when the diagnosis is difficult or an optical neuropathy is suspected [17, 18]. Computed tomography (CT) and magnetic resonance imaging (MRI) are useful to confirm the diagnosis through visualization of the muscle hypertrophy and the orbital fat, and also to assess the critical area of the orbital apex. Often the only finding is increased orbital fat, with resulting proptosis [20].

Therapeutic Approach

Patients are treated according to the degree of disease impairment, always having in mind that most

Fig. 36.1 Thyroid ophthalmopathy

Fig. 36.2 Another aspect of thyroid ophthalmopathy

patients display a mild disease with no progression during the follow-up. Graves' ophthalmopathy patients display hyperthyroidism reversal (when present), symptom relief, and decreased periorbital tissue inflammation [13, 21].

Symptom treatment comprises the use of artificial tears, raised head during sleeping hours, facial support when sleeping, and use of blinders that are often enough for symptom relief. Photophobia and sensitivity to wind or cold air can be reduced with sunglasses [13, 22]. Some studies suggest that use of selenium (100 μg 2×/day, over 6 months) may improve soft tissue edema, besides the implementation of quality-of-life measures, although such results require confirmation [23].

For patients with eye inflammation (red eyes) and increased diplopia and proptosis, a corticosteroid (prednisone 30 mg/day for 4 weeks) course should be started. If large doses are necessary they are intravenously administered. Cases whereby vision is lost, usually preceded by color vision loss, require the patient to immediately undergo corticosteroid therapy (intramuscular dexamethasone 4 mg, or prednisone 100 mg orally) and hospital admission for probable surgical decompression. Rituximab, radiation, and surgical decompression can be also used in select cases [13, 22, 24–26].

Pretibial Myxedema

The cutaneous manifestations of GD may result from excessive thyroid circulating hormone or from the autoimmune nature of GD [27, 28]. The most common clinical findings are ophthalmopathy, acropachy, and pretibial myxedema; the presence of the three findings make up the classic triad of GD, present in only 1% of cases [29].

Pretibial myxedema is a less often seen manifestation, present in only 5% of GD cases and in 15% of cases of patients with GD and ophthalmopathy [30]. About 90% of the patients with pretibial myxedema have hyperthyroidism and 10% are hypothyroid or euthyroid patients, although all of them display laboratory evidence of autoimmune thyroid disease [31]. About 50%

of the pretibial myxedema cases occur after the patient undergoes treatment for thyroidopathy either with radioactive iodine or thyroidectomy [32]. The ophthalmopathy is associated with most of the cases, usually coming before pretibial myxedema occurring within 1–2 years [31]. Its incidence has decreased possibly due to the early diagnosis and treatment implementation for GD. Contrary to what is prompted by its name, it is not limited to the pretibial area, and can reach the ankles and the feet dorsa, and be present in the elbows, knees, upper portion of the trunk and neck [33].

Etiopathogenesis

Pretibial myxedema results from glycosaminoglycan accumulation, specifically hyaluronic acid secreted by cytokine-stimulated fibroblasts. By showing the expression of the TSH receptor proteins by the dermis fibroblasts, the possibility arises that antibodies and/or T-cell-specific antigens start an inflammatory reaction that stimulates glycosaminoglycan production; excessive glycosaminoglycans are deposited in the dermis and the subcutaneous tissue [34–37].

Clinical Presentation

Pretibial myxedema is characterized by a bilateral asymmetric cutaneous thickening, usually with one or more less delimited papules or nodules that can display different diameters [37]. There is color variation from yellowish chestnut to violet, and an "orange skin" aspect due to the cutaneous thickening associated with the follicular prominence is frequently noticed [31, 37]. Lesions are usually asymptomatic although they can be pruritic or even painful [37]. Hyperpigmentation, hyperkeratosis, and hyperhidrosis may also be present. The most frequent sites include the medium and lower third of the pretibial region and, occasionally, the feet dorsa (Fig. 36.3). Other impaired regions are seldom noticed, although there are reports of atypical location, such as the fingers, hands, upper limbs, torso, shoulder, and face, albeit that in most of those reports there was history of trauma, vaccination, local scar, or surgery [31, 32, 37].
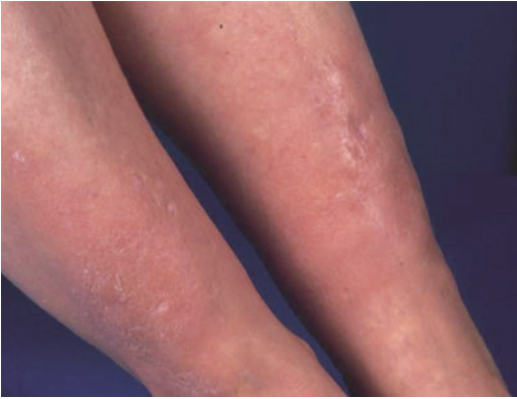
Fig. 36.3 Pretibial myxedema

The lesions usually develop along many months and then stabilize, or, in some cases, spontaneously recede [37]. Rarely the lesions evolve and reach the feet, hands, or legs, in such cases showing a more elephantiasis format [31, 32].

The differential diagnosis can be made with stasis dermatitis, cutaneous mucinosis (in lupus erythematosus, dermatomyositis, scleroderma), amyloidosis, hypertrophic lichen planus, and lipoid necrobiosis [33].

Complementary Examinations

The diagnosis of pretibial myxedema is based on the GD history and clinical characteristics of the lesion (location, nonpitting nature, and badly delimited margins). A biopsy is seldom necessary for the diagnosis, although it can be required when patients display disease-suggestive lesions but with no history of thyroid disease.

Therapeutic Approach

Most of the cases do not require treatment, with resolution occurring some years later. Treatment indications include pruritus, local discomfort, or aesthetic reasons. It is wise, nevertheless, to treat all new lesions so that they do not undergo a chronic process. Treatment encompasses minimization of the risk factors: quitting smoking, weight loss, and treatment of the disturbed thyroid. Improvement in thyroid function does not necessarily improve the myxedema [33]. As initial therapy, medium- to high-potency corticosteroids, with or without occlusion, are indicated; no improvement after 4–12 weeks of treatment leads to the use of intralesional corticosteroid, mainly for a presentation such as plaques and nodules [38]. Some authors support the use of compression stockings (20–30 mmHg) for lymphedema improvement [33, 37]. There are reports of pentoxifylline used in resistant cases [39]. Other reports mention rituximab and plasmapheresis in severely affected patients [40–43]. Immunoglobulin was effective in a series of noncontrolled cases [44]. When trauma is a precipitating factor of disease recurrence, surgical treatments must be avoided.

Thyroid Acropachy

The exact incidence of acropachy is not known, although estimates refer to 0.1–1% of GD patients [45].

Etiopathogenesis

Acropachy pathogenesis is similar to that of dermopathy. A research study investigated whether fibroblast activation in the periosteum and mucin deposition may be a triggering factor [46].

Clinical Presentation

Thyroid acropachy is a rare manifestation of thyroid autoimmune disease, present in extreme forms of dermopathy, and possibly showing finger or toe edema and clubbing. More seldom seen is acropachy together with distal arthritis [46]. It is part of the acropachy, pretibial myxedema, and ophthalmopathy triad [45].

Three manifestations of acropachy are noticed: finger and toe clubbing (88%); edema, and hardening of the skin of fingers and toes (20%); and presentation of arthritis and periostitis (10%) [46].

The most ordinary form of acropachy is digital clubbing, which occurs in 20% of dermatopathic patients. Digital edema and periosteal reaction in adjacent bone is the total clinical presentation, though less often seen. Thyroid acropachy always occurs in association with Graves' ophthalmopathy and thyroid dermopathy. Involvement of joints is unusual. Acropachy is not usually painful, although some patients have pain and function loss due to severe edema [45, 47].

Complementary Examinations

Skin biopsy shows typical pretibial myxedema findings, including fibroblast activation and glycosaminoglycan deposits [48]. The diagnosis is made with a combination of the thyroid disease history, clinical characteristics typical of ophthalmopathy and pretibial myxedema, and radiographic features of the hands and feet [45]. Fusiform edema of the soft tissues both in the patient's fingers and toes, and subperiosteal bone formation are radiographic findings. Subperiosteal reaction is uncommon in long bones [45–47].

Therapeutic Approach

There is no specific treatment available besides the basal immunologic treatment and management of the associated dermopathy. Painful acropachy periostitis requires use of anti-inflammatory agents [47].

Skin Manifestations of Hypothyroidism

Hypothyroidism, or a deficiency of thyroid hormone, is most often caused by a chronic autoimmune disease (Hashimoto's thyroiditis), but may also result from pituitary tumor or failure, iatrogenic thyroid ablation, goiter, or iodine deficiency [46].

Relatively common causes of primary hypothyroidism also include a prior history of therapy for hyperthyroidism, or a thyroidectomy (partial or total). External radiation given to the head, neck, or chest areas for lymphoma, for example, may also result in hypothyroidism [47].

Patients with hypothyroidism typically have cold, pale skin that is rough, dry, and scaly [10]. The skin may appear yellow because of carotenemia. The most characteristic skin change of hypothyroidism is myxedema, the accumulation of mucopolysaccharides in the skin. Patients seem to have puffiness around the eyes and swelling of the hands. There is often loss of the lateral third of the eyebrows, coarse brittle hair and nails, and generalized hair loss [48].

Cutaneous manifestations of Hashimoto's thyroiditis include acanthosis nigricans, alopecia, melasma, onycholysis, and vitiligo, among others [49].

The assessment of a hypothyroid patient requires a detailed history and physical examination. Many clinicians will also obtain a thyroid sonogram if there is a suspicion for nodules. Serum tests will include TSH initially (with T4 and T3 added if TSH is abnormal or if there is suspicion of central hypothyroidism), as well as measurement of thyroid peroxidase antibodies.

Once the diagnosis is made, the process involves levothyroxine administration, although it will not directly help the autoimmune-mediated aspects of the disease, such as pretibial myxedema and ophthalmopathy [50].

General Skin Manifestations and Generalized Myxedema

Endemic cretinism can result from iodine deficiency in the uterus, although it may result from the transplacental passage of substances that inhibit the production of thyroid hormones by interfering with iodine absorption in the thyroid gland (goitrogens). In 33% of children with congenital hypothyroidism, signs or symptoms of cutaneous abnormality are not found [51].

In Brazil, the bloodspot test ("Teste do Pezinho") is carried out up to the 30th day of life; it is now part of the Sistema Único de Saúde (SUS) (the publicly funded healthcare system) incorporated in 1992 (Portaria GM/MS no. 22, de 15 de Janeiro de 1992), with a legislation that made the test mandatory for all live newborns; it also includes assessment for phenylketonuria and congenital hypothyroidism [52].

Adult hypothyroidism develops insidiously, thus possibly persisting for many years. Adult hypothyroidism is a common type, more frequently occurring in women from 40 to 60 years old [51].

Generalized myxedema is a severe manifestation that may be seen in hypothyroidism, when mucin is deposited in the skin and other organs leading to a series of dermatologic and systemic changes [51].

Etiopathogenesis

There are no exact causes to determine the disease besides its association with low levels of thyroid hormones, associated with relevant dermal accumulations of mucopolysaccharides, mainly hyaluronic acid and chondroitin sulfate [51].

Clinical Presentation

Patients often display early tiredness, a feeling of fatigue, weakness, cramps mainly in the legs, and severe discomfort on cold days. The myxedema is characterized by typical periorbital swelling, thick lips, acral swelling, and widened tongue. Macroglossia may display a smooth and red aspect. The yellowish skin is explained by carotene accumulation in the stratum corneum (as result of the lesser hepatic conversion of β-carotene to vitamin A), and anemia [51, 53]. The carotenemia may be seen in hand palms and soles of feet, and nasolabial folds. Clavicular fat accumulation may be often noticed. The skin is dry, cold, and pale, mainly in the extension areas. Xerosis can be so severe that it may be considered a form of acquired ichthyosis. It becomes pale because of the higher levels of water and mucopolysaccharides in the dermis, which change the light refraction. It also shows a peripheral vasoconstriction that may determine features of cutis marmorata. Hypohidrosis is also noticed. The palms may become significantly drier, possibly mimicking an acquired keratoderma. The skin is diffusely swollen and becomes sturdy when touched. Despite the edematous aspect, the skin is not depressed if pressure is applied upon it. The presence of cutaneous edema may be partially explained by the hygroscopic characteristics of the mucopolysaccharides, although an increase in the transcapillary escape of albumin was shown, possibly resulting in its extravascular accumulation, thus playing a part in this edema. In addition, inappropriate lymphatic drainage can account for the development of exudates in the serous cavities that become visible in the myxedematous state [51–54].

Body and head hair may be dry and brittle. Hair loss results in partial alopecia. Irregular alopecia plaques can be noticed with persistent lanuginous hair. The eyebrows exhibit a characteristic loss of the lateral third bilaterally. Hair growth is slow. Patients with spontaneous or iatrogenic myxedema may also show a greater amount of hair in the telogen phase. This may indicate that the hypothyroidism alopecia is being mediated by hormonal effects [51–54].

The nails show a slow growth and a fragile structure.

In the myxedematous state wound scarring can be impaired, thus determining such a slow process. Purpura may sometimes be noticed as a consequence of the decrease in clotting factor, or loss of vascular support resulting from the presence of mucin in the dermis may be seen [53, 54].

Some reported uncommon observations in the literature can be deduced as actual manifestations of the hyperthyroid state. A manifestation similar to ectodermal dysplasia, possibly inherited in a recessive autosomal manner, was reported by the acronym ANOTHER (alopecia, ungual dystrophy, ophthalmologic complications, dysfunctional thyroid, hypohidrosis, ephelides and enteropathy, and respiratory tract infections) [51].

The systemic manifestations of hypothyroidism are numerous and are not covered in this chapter. It is important to know that mucin deposition also occurs in many organs other than the skin, such as the heart, intestines, and the kidneys, resulting in functional outcomes.

Complementary Examinations

The diagnosis is clinically suspected and confirmed by the low levels of free circulating T4. The TSH serum level is high in primary hypothyroidism and low in secondary hypothyroidism. Myxedema is not seen in secondary hypothyroidism [53, 54].

The anatomopathologic examination shows a mild epidermal hyperkeratosis and development of corneal plugging in the pilous follicles, and small dermal deposits of mucopolysaccharides. In the most noticeable cases edema is seen with separated collagen bundles. In some cases preeminent amounts of dermal mucin can be noticed, mainly perivascular and perifollicular. The number of elastic fibers is decreased [53].

Therapeutic Approach

If the impairment happens in newborns, immediate treatment is crucial for their appropriate mental development. This important treatment begins before the 4th month of life [53, 54].

Whatever the situation, symptoms recede when the therapy employs thyroxine.

Skin Manifestations Related to the Thyroid Gland and Not to Its Function

Thyroglossal Duct Cyst

Thyroglossal duct cyst results from a failed obliteration of the duct developed in the embryogenesis during thyroid migration, and represents the most common median line cyst. Ectopic neoplasias of the thyroid tissues are rare, and rarer if associated with this duct [55].

Etiopathogenesis

In the fourth week of fetal development the thyroid tissue is located in the pharyngeal floor, and through the thyroglossal duct this tissue migrates into its usual position in the thyroid. During the thyroid descent, the gland keeps its connection to the base of the tongue through the thyroglossal duct, and when migration is concluded the duct is obliterated at around the 8th gestational week. This channel persistence is called remnant thyroglossal duct [56].

This congenital remnant is usually noticed as a cyst coated with a secretory epithelium. Both men and women can show this condition, which can be located anywhere in the thyroglossal duct, found in 60% of the cases between the hyoid bone and the thyroid cartilage; 24% suprahyoid; 13% substernal; and 2% intralingual [57].

The diagnosis is made up to 10 years of age in about 30% of the cases; from 10 to 20 years of age in 20%; from 20 to 30 years of age in 15%, and after 30 years of age in 35% of cases. Ectopic thyroid tissue is seen in 62% of cases and is subject to the same pathology of the thyroid itself [56].
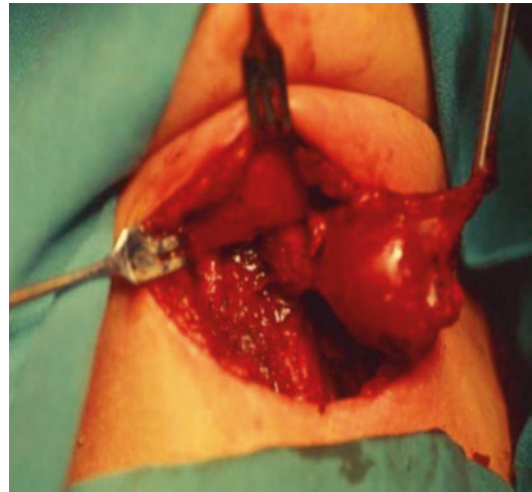
Fig. 36.4 Thyroglossal duct cyst

Clinical Presentation

The clinical presentation shows a nodular lesion of cystic consistency at the medium line of the neck at the level of the thyroid membrane. Cyst infection may happen simultaneously with episodes of airway infection, and signs of local inflammation can be seen (Fig. 36.4). A fistula secondary to the cyst infection may also be apparent [58].

Complementary Examinations

Ultrasonography of the cervical region is the method used to identify the cyst, with an accuracy of 90% [58]. When facing a doubtful diagnosis, an aspiration puncture can be conducted to confirm the presence of thyroid tissue.

Therapeutic Approach

The treatment of choice is cyst removal performed using the Sistrunk technique, comprising removal of the central part of the hyoid bone. If infection is ascertained, the use of systemic antibiotics may be necessary [36].

Thyroid Cancer and Cutaneous Metastases

Thyroid papillary carcinoma accounts for most of the cases of cancers of this type in children,

usually occurring as metastases in regional lymph nodes. Papillary carcinoma is made up of Hürthle cells, usually noticed in middle-aged and elderly persons. Among the elderly population, the most common metastases are distant metastases. On the other hand, tumors of undifferentiated cells are characteristic of older people, and may predispose distant metastases besides involvement of regional lymph nodes [56].

Cutaneous metastasis is a rare event [60]. In a series of 724 patients, thyroid metastatic carcinoma accounted for less than 1% of the cutaneous metastases [61], and no thyroid metastasis was noted in a series of 4020 individuals with cutaneous metastases [62].

Etiopathogenesis

Thyroid follicular carcinoma displays metastatic dissemination mainly through hematogenous spread, which occurs in 10–15% of cases of more advanced tumors. The most often affected sites include the bones and the lungs, and less frequently the brain, liver, bladder, and skin.

In 2005 Quinn et al. described four patients with thyroid cutaneous metastasis, three men and one woman, with a medium age range of 64 years, all of whom had invasive thyroid follicular carcinoma [60]. Two of these patients displayed scalp metastases: one in the neck, and another in the sacral skin. In three cases the specific morphology and immunohistochemistry were conducted, revealing that one of these patients showed primarily spinal metastasis of characteristic morphology, although he underwent anaplastic change after treatment. Including these four cases a total of 14 were reported in the literature, with cutaneous metastasis of thyroid follicular carcinoma in most patients: that is, 10 out of 14 patients had primary site histopathology [60].

Clinical Presentation

The morphology of cutaneous metastases is variable. The lesions may manifest as macules, plaques, papules or nodules. They can imitate other conditions, such as alopecia, infections (erysipelas and paronychia), benign cysts (epidermoid or pilar), pyogenic granuloma, and

Fig. 36.5 Thyroid papilliferous carcinoma

cutaneous malignant neoplasias (basal cell carcinoma and keratoacanthoma) [63–65].

Cutaneous manifestations common to the thyroid papilliferous carcinoma are nodules in the scalp and neck [63, 66, 67], and lesions in the scar of thyroidectomy [68]. A metastatic tumor at the site of thin-needle aspiration biopsy was also noticed by Tamiolakis et al. [67]. Cutaneous metastases of thyroid papillary carcinoma have also been described on the abdominal wall, arms, buttocks, thoracic wall, face, shoulders, and thighs [60] (Fig. 36.5).

Cutaneous thyroid metastases can occur after an early diagnosis of thyroid cancer, thus making the cutaneous lesion diagnosis easier, as well as being the first identified manifestation of the pathology. Since cutaneous lesions are accessible to clinical examination and patient visualization, they may easily trigger the investigation leading to the primary site of the neoplasia.

Complementary Examinations

Complementary examinations are crucial to the proper identification of the cutaneous metastases because they allow the identification of the lesion's primary site.

Anatomopathologic examination of cutaneous metastases of papilliferous carcinoma and thyroid follicular carcinoma also show characteristics similar to those of the primary site. Immunohistochemistry may be also useful for diagnostic confirmation and exclusion of tumors originating in other organs.

Thyroid papillary and follicular carcinomas express the thyroid transcription factor 1 (TTF-1) and thyroglobulin (a glycoprotein synthesized in the cytoplasm of the thyroid follicular cells, and detected in 95% of papillary carcinomas) [69].

Therapeutic Approach

The therapeutic approach is determined according to clinical staging of the neoplasia. Management includes a partial or total thyroidectomy followed by adjuvant radiotherapy to treat invasion of the cervical region. It can be associated with chemotherapy with isolated doxorubicin, or associated with other chemotherapeutic agents, as well as the use of radioactive iodine. Molecular targeted therapy aimed at specific receptors has shown promising outcomes.

The prognosis for patients with thyroid metastatic papilliferous carcinoma of the skin is usually unfavorable [64, 66]. There are, nevertheless, individuals with thyroid cutaneous metastases who survived many years after the diagnosis [68, 66, 70]. Furthermore, with the advent of molecular targeted therapies, such as tyrosine kinase inhibitors, the prognosis for patients with metastatic disease, and mainly for those with a rearrangement during aberrant transcription of the oncogenesis (RET), is better than the observed prognosis in individuals with thyroid papilliferous carcinoma who underwent treatment before the discovery of these agents [71].

Glossary

Cutis marmorata Manifests as skin changes displaying violet spots on the trunk and limbs, which can be highlighted by cold temperature.

Diplopia The condition when an individual sees two images of the same object.

Glycosaminoglycans Components of the connective tissue. They represent 30% of the body's organic material and can exist as different types, such as chondroitin sulfate for cartilage, bone, or cornea; dermatan sulfate for the dermis and the tendons; and heparan sulfate for the liver, lungs, and aorta.

Hyaluronic acid A biopolymer made of the glucuronic acid and *N*-acetylglucosamine. With a viscous texture, it exists in the synovial fluid, the vitreous humor, and the connective tissue of numerous organisms, being an important glycosaminoglycan in articulation composition.

Lymphedema The accumulation of interstitial fluid rich in proteins of high molecular weight.

Macroglossia The abnormal growth of the tongue so that it reaches a size larger than the one allowed by the buccal cavity, resulting in impaired phonation and respiratory, suction, and/or swallow function.

Plasmapheresis An extracorporeal process by which the blood collected from a patient is separated into its plasma and cell element compounds.

Proptosis Proptosis is characterized by a displacement of the eyeball to the front of one eye, or both eyes.

Proto-oncogene (RET) RET proto-oncogene activating mutations may result in the development of the thyroid medullary carcinoma. Its research study is useful for the genetic tracking of thyroid medullary carcinoma.

Radioactive iodine Radioactive iodine treats hyperthyroidism by gradually shrinking the thyroid, ultimately destroying the gland.

Rituximab A monoclonal chimeric antibody (murine/human) against an antigen that is the protein of the cell surface, CD20

Thyroxine (T4) A hormone that plays a role in several body functions, including growth and metabolism.

Tri-iodothyronine (T3) T3 and T4 (thyroxine) are hormones produced by the thyroid gland. They help to control the rate at which the body uses energy, and are regulated by a feedback system.

Thyroid-stimulating hormone (TSH) TSH stimulates the production and release of T4 (primarily) and T3. As necessary, T4 is converted to T3 by the liver and other tissues.

Thyroid transcription factor 1 (TTF-1) TTF-1 regulates the transcription of the specific genes of the thyroid, the lung, and the diencephalon. It is used in anatomic pathology as a marker to determine whether a tumor has its origin in the lung or the thyroid.

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Dyslipidemias

37

Cristiane Almeida Soares Cattani and Renata Heck

Key Points

- Dyslipidemias may be associated with xanthomas and cardiovascular, pancreatic, and cerebrovascular diseases
- Xanthomas must alert the clinician to dyslipidemias or underlying diseases, especially in children
- Xanthelasma may appear in normolipemic patients
- Tendinous and tuberous xanthomas can be a cutaneous sign of severe familial hypercholesterolemia or systemic diseases
- Management of dyslipidemia involves treating associated disorders and exacerbating factors with a multidisciplinary approach and oral medication
- Early diagnosis of xanthomas and prompt treatment of associated dyslipidemic disorder prevents later systemic complications.

Introduction

Dyslipidemia represents any disorder of lipoprotein metabolism: "dys-" + "lipid" (fat) + "-emia" (in the blood) = disordered lipids in the blood. It confers an increased risk of cardiovascular disease, cerebrovascular disease, pancreatitis, and xanthoma, which are the characteristic skin manifestations in hyperlipoproteinemia (HLP).

Xanthomas consist of the accumulation of lipid-rich macrophages known as foam cells. They do not represent a disease but rather are signs of different lipoprotein disorders. They also may arise without an underlying metabolic defect [1].

Early diagnosis and treatment of dyslipidemias may have a significant impact on the prevention and prognosis of a patient's disease. It can therefore be considered a relevant concern in the public health context.

General Epidemiology

Hyperlipidemia is very common in the general population. Hypercholesterolemia can be defined as a low-density lipoprotein (LDL) cholesterol level greater than 160 mg/dl. It is estimated that more than 100 million people in North America alone have an elevated serum level >200 mg/dl [2].

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A high prevalence of dyslipidemias also exists in Brazil. A survey of 49,395 adults living in several Brazilian cities and federal districts showed a dyslipidemia rate of approximately 16.5% [3].

Hypercholesterolemia is therefore fairly common, and most affected individuals have a mild form. However, there are also more severe forms such as familial hypercholesterolemia, an autosomal dominant disease with a somber cardiovascular prognosis. Its prevalence is traditionally 1 in 500, but a recent study in the United States showed an overall nationwide prevalence of 1 in 299 [4].

Although a significant number of people suffer from hyperlipidemia, only a minority will develop cutaneous xanthomas, the exact mechanism of which is not completely understood [2].

Etiopathogenesis

There are two pathways of lipid metabolism: exogenous and endogenous. In the exogenous pathway dietary lipids are absorbed into the intestinal epithelium after been degraded by pancreatic lipase and bile acids to fatty acids and monoglycerides. After absorption, triglycerides are repackaged with cholesterol esters to form the central core of a chylomicron that is surrounded by phospholipids, free cholesterol, and apolipoproteins (ApoA-I, ApoB-48, ApoC-II, and ApoE). These chylomicrons enter the lymphatic circulation and are hydrolyzed by the action of lipoprotein lipase (present in capillary walls) and its cofactor ApoC-II, releasing free fatty acids. These free fatty acids are used as an energy source or stored in adipose tissue.

The endogenous pathway begins in the liver with very LDL (VLDL) synthesis from hepatic triglycerides and circulating free fatty acid. VLDL particles also contain apolipoproteins (ApoB-100, ApoC, and ApoE). Circulating VLDL interacts peripherally with lipoprotein lipase (LPL), which hydrolyzes VLDL, removing triglyceride content. A residual particle called the VLDL remnant is degraded by the liver after bind ApoB-100 and ApoE receptors. A portion of VLDL remnant interacts with hepatic lipases and is converted into LDL. LDL particles enter the circulation and can be converted to bile acids or used by nonhepatic tissues to produce hormones in cell membrane synthesis, or can be stored.

High-density lipoprotein (HDL) produced in liver and intestine removes the excess cholesterol from peripheral tissues. The cholesterol is esterified to cholesterol esters by the enzyme lecithin:cholesterol acyltransferase (LCAT) after its activation by ApoA-I. HDL transfers the cholesterol esters to LDLs or VLDLs for transportation back to the liver and conversion to bile acids.

Defects in lipoprotein lipase, receptors, apolipoproteins, or cofactors may interfere in the pathway at different times. If the disturbance results in elevation of triglyceride-rich particles, eruptive xanthoma can occur. Xanthelasma, tuberous xanthomas, or tendinous xanthomas occur if the defect results in accumulation of cholesterol-rich particles.

The mechanism of cutaneous lesion formation is not completely understood. Serum lipid seems to infiltrate tissues where they are phagocytosed by macrophages to form lipid-laden foam cells [5].

Clinical Presentation

Xanthomas may present with a variety of morphologies, from macules and papules to plaques and nodules, but the major distinguishing feature of the lesions is the yellow to orange hue.

The morphology and anatomic location of the lesions can suggest the presence of an underlying lipid disorder or a paraproteinemia.

Most cutaneous xanthomas do not appear before adulthood, except in the homozygous form of familial hypercholesterolemia (type II).

Table 37.1 Important types of hyperlipoproteinemias and xanthomas

Type of hyperlipoproteinemia	Type of xanthoma	Laboratory	Systemic manifestations
Type I	Eruptive	Chylomicrons/VLDL ↑	No increased risk
		Triglycerides ↑	Cardiovascular disease
Familial LPL deficiency		LDL ↓	
Familial hyperchylomicronemia		HDL ↓ or normal	
Type II	Plane xanthoma	Cholesterol ↑	Atherosclerosis of peripheral and coronary arteries (premature cardiovascular disease)
Familial hypercholesterolemia	Xanthelasma	Reduced LDL clearance	
Heterozygous	Intertriginous areas		
Homozygous	Interdigital		
Familial defective ApoB-100	Tendinous		
	Tuberous		
	Tuberoeruptive		
	Early appearance (first decade)		
Type III	Plane xanthoma	Cholesterol ↑	Atherosclerosis of peripheral and coronary arteries (premature cardiovascular disease)
Familial dysbetalipoproteinemia	Palmar creases[a]	LDL ↑	
Remnant removal disease	Xanthelasma	VLDL ↑	
Broad beta disease	Tuberoeruptive	Triglycerides ↑	
ApoE deficiency	Tuberous		
	Tendinous		
Type IV	Eruptive	VLDL ↑	Often associated with:
Endogenous familial hypertriglyceridemia		Triglycerides ↑	Type II non-insulin-dependent diabetes
			Obesity
			Secondary hypertriglyceridemia (from medications, alcoholism)
Type V	Eruptive	Triglycerides ↑	Diabetes mellitus
		Chylomicron/VLDL ↑	

LPL lipoprotein lipase, *VLDL* very-low-density lipoprotein, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein

[a]Characteristic

Clinical types of xanthomas include eruptive, tuberous, tuberoeruptive, tendinous, planar (xanthelasma), and verruciform [2].

In 1965, Lees and Frederickson published a system for phenotyping various disorders of lipid metabolism based on electrophoretic migration of the serum lipoproteins present. This is still used today in a modified form.

The clinical presentations of the various changes in lipid metabolism are summarized in Table 37.1.

Eruptive Xanthomas

Eruptive xanthomas are small reddish-yellow papules, from 1 to 5 mm in diameter, arising sud-

Fig. 37.1 Eruptive xanthoma. Multiple small reddish-yellow papules

denly in crops over the buttocks, thighs, and the extensor surfaces of the arms, hands, and legs [1] Fig. 37.1.

They are usually associated with primary or secondary hypertriglyceridemia. Triglyceride levels usually exceed 3,000–4,000 mg/dl.

Eruptive xanthomas usually appear in Frederickson classification type I (elevated chylomicrons), type IV (elevated VLDL), and type V (elevated chylomicrons and VLDL).

Elevated triglycerides may be due to deficient activity of enzymes, as in lipoprotein lipase deficiency (chylomicronemia) or dysfunctional ApoC-II, or in other controlling factors such as impaired insulin activity. Hepatic overproduction of VLDL as a result of a genetic defect that causes an abnormal response to dietary carbohydrates and insulin is defined as Frederickson type IV (endogenous familial hypertriglyceridemia).

Secondary acquired defects in lipoprotein lipase activity, such as those due to uncontrolled diabetes mellitus, often occur in these patients, aggravating the handling of dietary lipids and also leading to elevated chylomicrons (Frederickson type V).

Besides diabetes, hypothyroidism and other conditions such as obesity, pregnancy, and alcohol abuse may impair triglyceride metabolism. This can also be attributed to oral estrogen replacement and other systemic medications (e.g., retinoids, cyclosporine, olanzapine, and protease inhibitor therapy) [1, 2].

In genetically predisposed patients, hypertriglyceridemia induced by isotretinoin therapy seems to correlate with a future risk of metabolic syndrome.

The Koebner phenomenon has been reported to occur with eruptive xanthomas. It emerges frequently, accompanied by tenderness and pruritus (an inflammatory halo may appear in early disease). There are reports of eruptive xanthomas appearing in a patient's old tattoos [6].

Remission of eruptive xanthomas depends on diagnosis and treatment of the underlying primary or secondary disorder in order to lower the triglyceride levels.

Tuberous/Tuberoeruptive Xanthomas

Tuberoeruptive and tuberous xanthomas are often described together because they are clinically and pathologically related. Tuberoeruptive xanthomas appear on extensor surfaces as yellowish or reddish papules or nodules, especially on the elbows and knees. They also may be located in knuckles, buttocks, and other sites (Figs. 37.2 and 37.3).

Fig. 37.2 Tuberous xanthoma. Multiple yellowish nodules in cervical region (Courtesy of Dermatology Department of Federal University of Health Science, Porto Alegre)

Fig. 37.3 Tuberous xanthoma. Solitary yellowish nodule in axillary region (Courtesy of Dermatology Department of Federal University of Health Science, Porto Alegre)

Tuberous lesions are larger than tuberoeruptive lesions (diameter >3 cm). Both are present in hypercholesterolemic states, with cholesterol and triglyceride serum levels elevated (Frederickson type II and type III).

Dysbetalipoproteinemia (type III) is a genetic disorder of lipid metabolism caused by the presence of an isoform of ApoE, mainly ApoE2, a poor ligand for the high-affinity ApoB-100/E receptor which results in decreased hepatic uptake of chylomicrons and VLDL remnants. Its consequence is high serum levels of cholesterol and triglycerides. In 80% of patients tuberous or tuberoeruptive xanthomas are present. Plane xanthomas of the palm creases (*xanthoma striatum palmare*) may also appear and have characteristic cutaneous features.

Affected patients have an increased risk of developing premature cardiovascular disease, gout, and diabetes.

Unlike eruptive xanthomas, tuberous lesions do not involute as quickly with appropriate therapy [2].

Very rarely tuberoeruptive, planar, and palmar xanthomas have been noticed in severe HDL deficiency (HDL levels <10 mg/dl) or in patients with multiple myeloma and monoclonal gammopathies [7].

Tendinous Xanthomas

These xanthomas are firm subcutaneous nodular lipid deposits that may be found in fascia, ligaments, Achilles tendons, or extensor tendons of hands, elbows, and knees. The appearance of the overlying skin is normal. Ultrasonography can aid the diagnosis by showing hypoechoic nodules or an increase in the anteroposterior diameter of the tendon [8].

Tendinous xanthomas are usually related to markedly elevated levels of cholesterol (>300 mg/dl) [7].

The rate and growth of xanthoma deposition is associated with the duration and severity of LDL levels [7]. Triglyceride and HDL levels are typically normal.

Dysbetalipoproteinemia and hypothyroidism may present with tendinous xanthoma.

However, the most frequent lipid disorder associated with this form of xanthoma is familial hypercholesterolemia (Frederickson type II). This condition is inherited in an autosomal dominant fashion with a high degree of penetrance. Deficiency of normal LDL receptors on cell membranes leads to poor hepatic clearance of circulating LDLs and, therefore, elevated cholesterol levels, with widespread atherosclerosis and premature cardiovascular disease (age <60 years). Xanthomas appear in the first decade of life. Plane xanthomas of the interdigital spaces of the fingers are considered pathognomonic for the homozygous state. Heterozygotes are more common (as mentioned in Epidemiology). Besides tendinous xanthomas, tuberous, tuberoeruptive, and planar xanthomas (including xanthelasma) also may be seen in this disorder.

Another closely related genetic disease is familial defective ApoB-100. Although the LDL receptor is normal, there is a poor affinity of LDL for this receptor because the mutation affects its ligand, ApoB-100. The clinical findings are very similar to those of familial hypercholesterolemia, though less severe.

Rarely, tendinous xanthomas can develop in the absence of a lipoprotein disorder.

Cerebrotendinous xanthomatosis is a rare condition in which despite modest elevations of cholesterol levels there are abnormal cholestanol deposits in tendons and brain tissue, with risk of neurologic disease including cerebellar ataxia and dementia [7]. This disorder results from an enzymatic defect in the bile acid synthetic pathway, leading to the abnormal accumulation of an intermediate known as cholestanol (a physiologic sterol normally found in lower concentrations than cholesterol).

In β-sitosterolemia (phytosterolemia) there is abnormal accumulation of plant sterols with tendinous xanthoma formation and premature cardiovascular disease. Normally, these sterols are eliminated efficiently back to the intestinal lumen by intestinal transporters, but defects in this transport leads to retention of these sterols in the intestinal cell and their secretion on chylomicrons in the plasma space [7].

Plane Xanthomas and Xanthelasma

Plane xanthomas are clinically described as yellow to orange macules, soft papules, patches, or plaques. They can be circumscribed or diffuse and are commonly found in eyelids (xanthelasma), wrists, palms, and intertriginous areas.

They are non-inflammatory, mostly asymptomatic, and their location can help to address the underlying lipid disorder. For instance, intertriginous plane xanthomas that appear in the antecubital fossae or the interdigital spaces are almost pathognomonic for homozygous familial hypercholesterolemia.

Plane xanthomas of the palmar creases (xanthoma striatum palmare) associated with tuberous xanthomas are potentially diagnostic for dysbetalipoproteinemia.

Other systemic diseases may present with xanthomas. In biliary atresia, primary biliary cirrhosis, and conditions with prolonged obstruction of the biliary tree, unesterified cholesterol accumulates in blood, leading to xanthoma formation. They begin as localized beige-orange plaques on the hands and feet, but can become generalized. Patients often present with jaundice, pruritus, and hyperpigmentation of skin.

Plane xanthomas also occur in normolipemic patients (i.e., with normal lipid levels). However, in some cases they have been observed in patients with multiple myeloma, lymphoma, leukemias, and underlying monoclonal gammopathy. In this disorder, monoclonal immunoglobulin G is thought to bind circulating LDL, rendering the antibody–LDL complex more susceptible to phagocytosis by macrophages [9].

Xanthelasma, or xanthelasma palpebrarum, is the most frequent plane xanthoma, characteristic of the eyelids. It can be present even in the absence of a lipid disorder. Elevated LDL cholesterol levels are found in only about one-half of the patients with lesions, but in younger people with xanthelasma and family history of dyslipidemia the lipid profile must be investigated (Fig. 37.4).
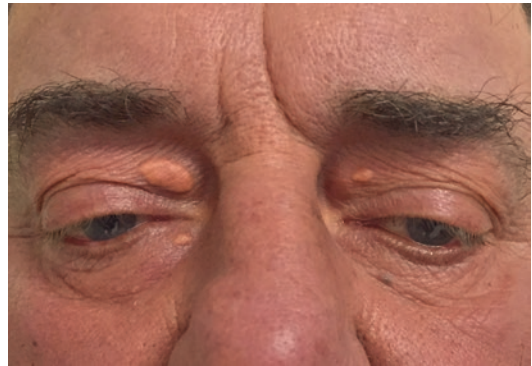
Fig. 37.4 Xanthelasma. Yellow patches on the eyelids

Verruciform Xanthomas

Verruciform xanthomas are planar or verrucous solitary plaques ranging from 1 to 2 cm in diameter. They occur primarily in the oral cavity (mouth) but sometimes in anogenital (including the scrotum) or periorificial sites.

Usually they are asymptomatic and persist for years. This form of xanthoma is not associated with any dyslipidemia but may be seen in lymphedema and in the setting of other diseases such as epidermolysis bullosa, discoid lupus erythematosus, and graft-versus-host disease (GVHD).

Nonmucosal verruciform xanthoma is the characteristic lesion in congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome.

Histologically there is usually hyperkeratosis, acanthosis, papillomatosis, and foamy macrophages limited to the submucosa or dermal papillae. Therefore, these xanthomas may be confused with warts and other papillomatous conditions, because the few foam cells beneath the epithelium may be subtle and easy to miss [2, 7].

Xanthomas in Children

In children, xanthomas are uncommon and appropriate investigation is mandatory. If laboratory screening reveals a hyperlipidemia, early intervention must be considered.

The most common dyslipidemias are types IIA, IIB, and IV. Type I and type III HLP are extremely rare in pediatric patients, and type V is uncommon.

As in adults, hyperlipidemias often may be secondary to obesity, hypothyroidism, diabetes mellitus, nephrotic syndrome, or, more rarely, genetic disorders. In these situations xanthomas may develop during childhood [2]. When they occur in children and adolescents (especially tuberous), a more severe form of hyperlipidemia should be suspected [10].

The differential for xanthomas in children includes homozygous familial hypercholesterolemia, β-sitosterolemia, cerebrotendinous xanthomatosis, type I glycogen storage (Von Gierke) disease, and Alagille syndrome. In children Alagille syndrome is an inherited syndrome of biliary hypoplasia leading to elevated serum cholesterol. These patients have a characteristic facies with a prominent forehead, hypertelorism, pointed chin, and nasal dystrophy. Xanthomas may be seen in flexures, elbows, knees, and palms or fingers. Serum cholesterol is elevated when patients are young but can decrease over time. Nearly 12% of patients with this syndrome develops cirrhosis. Treatment consists of medical management. If cirrhosis develops, liver transplantation is indicated, after which xanthomas have been found to resolve [7].

Most cases of type I HLP are caused by congenital deficiency of LPL, congenital deficiency of ApoC-II, or an LPL inhibitor (e.g., an anti-LPL autoantibody).

In one study of patients with LPL deficiency, 80% presented xanthomas before 10 years of age. In contrast, Apo-CII deficiency is usually diagnosed later in life (>13 years old). ApoC-II deficiency rarely presents in infancy [11].

In children, LDL cholesterol concentrations of 130 mg/dl or higher define type IIA HLP. The plasma is clear in this type because LDL particles are not large enough to scatter light, as opposed to VLDL or lipoprotein remnants that are large enough to cause turbidity.

In type IIB HLP, triglyceride levels are elevated to 125 mg/dl or higher, and LDL cholesterol levels are also elevated. If the triglyceride level is typically 300–400 mg/dl or higher, the plasma appears turbid (lipemic).

Hypertriglyceridemia (usually the type IV HLP phenotype) is frequently observed in children with obesity, diabetes, or both conditions. Familial hypertriglyceridemia is rarely expressed in childhood unless another underlying cause of hypertriglyceridemia is present [11].

The differential diagnosis of the various clinical presentations of xanthomas are listed in Box 37.1.

Box 37.1 Differential Diagnosis of Xanthomas

Xanthelasma:
  Sebaceous hyperplasia
  Syringoma
  Adnexal neoplasms
  Periocular xanthogranuloma
  Palpebral sarcoidosis

Plane xanthomas:
  Amyloidosis
  Pseudoxanthoma elasticum
  Sarcoidosis

Eruptive xanthomas:
  Xanthoma disseminatum
  Disseminated granuloma annulare
  Sarcoidosis
  Generalized eruptive histiocytomas
  Non-Langerhans cells histiocystosis
  Xanthomatous lesions of Langerhans cells histiocytosis
  Juvenile xanthogranuloma (micronodular form)

Tuberous or tendinous xanthomas:
  Cysts
  Lipoma
  Neurofibroma
  Erythema elevatum diutinum
  Rheumatoid nodule
  Subcutaneous granuloma annulare

Complementary Examinations

Patients seeking a dermatologist because of xanthomas must be evaluated for an underlying dyslipidemia and referred to the specialist.

Lipid Profile

The standard lipid profile consists of direct measurement of total cholesterol, HDL cholesterol, and triglycerides, with a calculated LDL cholesterol, obtained after a 9-h to 12-h fast.

Metabolic Profile

Since hypertriglyceridemia with low HDL and elevated LDL is indicative of insulin resistance, metabolic screening is recommended with fasting glucose, serum creatinine, hepatic panel, thyroid function tests, and urinary protein [7].

Skin Biopsy/Histopathology

If the diagnosis of xanthomas is in doubt, obtaining a biopsy of the suspicious lesions will reveal accumulations of fat (not cholesterol).

The characteristic histologic finding in xanthomas is the foam cell. This is a macrophage that contains lipid. Dermal infiltrates of lipid are seen in all xanthomas but may vary in the degree of lipid content, the inflammatory infiltrate, the amount and location of the infiltrate, and the presence of extracellular lipid. Laboratory processing must take care not to remove deposits of lipid from the tissue sample and leave artifactual clefting in the histological appearance. Since cholesterol esters are doubly refractile, polarized microscopy is very useful (Fig. 37.5).

Early in lesion development, foam cells are relatively small in number and size. The initial inflammatory infiltrate is mixed, containing both neutrophils and lymphocytes. As increased lipidization occurs as the appearance of the lesion becomes more typical of a xanthoma, but foam cells remain fewer in number when comparing eruptive with other forms of xanthomas.

Extracellular lipids are present in the dermis, which is seen as artifactual clefts filled with a wispy, faint blue-gray material.

Tuberous xanthomas reveal foam cells and cholesterol clefts (fibrosis is often noticed but without a large number of inflammatory cells). Tendinous xanthomas are similar, but with larger foam cells.

Xanthelasmas (the common type of plane xanthoma) can be differentiated by their unique
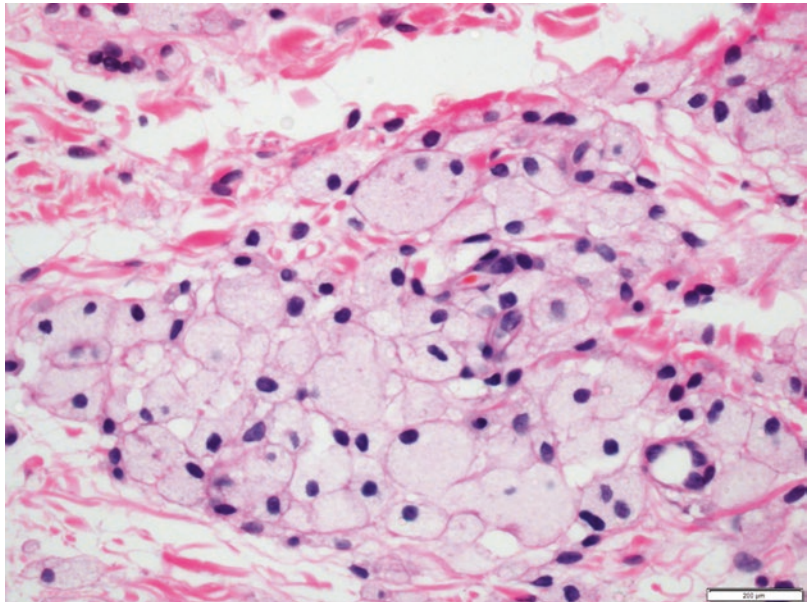
Fig. 37.5 Xanthoma histopathology. Dermal foam cells (macrophages with lipid content) (×400)

histologic appearance: along with foam cells, they may reveal striated muscle fibers, vellus hair, and/or a thinned epidermis (characteristic of the eyelids) indicative of its superficial location. There are no inflammatory cells and minimal fibrosis may be seen [2].

Therapeutic Approach

Management of dyslipidemia involves treating associated disorders and exacerbating factors such as obesity, smoking, and diabetes. It is often necessarily a multidisciplinary approach. Therapeutic lifestyle changes include aerobic exercise, dietary modifications (decreased intake of saturated or *trans* fatty acids), achievement of ideal body weight, and reduced alcohol consumption [2, 7, 12].

When pharmacologic intervention is necessary, statins are the drugs of choice for the initial treatment of dyslipidemia, and have been shown to reduce cardiovascular mortality significantly. Statins competitively inhibit HMG CoA reductase, blocking cholesterol biosynthesis. These drugs mainly act by lowering LDL cholesterol, but also by decreasing VLDL and triglycerides and raising HDL cholesterol levels [13, 14]. The most important adverse effects include elevations in hepatic transaminases and muscle toxicity. A baseline creatine kinase (CK) level should be obtained for reference, but there is no evidence for routinely monitoring muscle enzymes [2, 14]. Concomitant use with cyclosporine, fibrates, macrolides, azole antifungals, and protease inhibitors is contraindicated because of the increased risk of rhabdomyolysis.

Fibrates are the drugs of choice in the treatment of hypertriglyceridemia, and act by reducing hepatic secretion of VLDL and stimulating lipoprotein lipase activity in peripheral tissues. Fibrates are not associated with statins because of the increased risk of muscle toxicity. They can also interfere with warfarin; the anticoagulant

dose should be reduced when such an association exists. Available drugs of this class include bezafibrate, ciprofibrate, fenofibrate, and gemfibrozil [13, 15].

Nicotinic acid is one of the oldest drugs used for the treatment of dyslipidemia. It inhibits hepatic synthesis of VLDL and, consequently, LDL levels. There is also an increased activity of lipoprotein lipase, reducing triglyceride levels. HDL levels increase with nicotinic acid. Flushing is a common side effect that limits its use.

The bile acid sequestrants (cholestyramine) bind bile acids, preventing them from being reabsorbed in the intestine. They are effective in the treatment of heterozygous familial hypercholesterolemia but can increase triglyceride levels. The major side effect is gastrointestinal discomfort. Cholestyramine can impair the absorption of coadministered medications such as warfarin, digoxin, levothyroxine, and fat-soluble vitamins, administration of other drugs 1 h before or 4 h after cholestyramine intake being indicated [16].

Ezetimibe inhibits dietary and biliary cholesterol absorption in the intestine without affecting the absorption of fat-soluble drugs. It shows no significant gastrointestinal symptomatology and presents no significant interaction with statins [17].

Drug treatment of dyslipidemia is summarized in Table 37.2.

Lipid disorder correction leads to resolution of xanthomas in many patients. Eruptive xanthomas tend to disappear faster than tuberous or tendinous xanthomas. The latter may require months to years of systemic treatment. Unresponsive xanthomas can be treated with surgery or locally destructive methods [18].

Regarding xanthelasma, many techniques have been described, such as trichloroacetic acid application, cryosurgery, surgical excision, electrocauterization, and laser ablation [19]. Xanthelasma tends to recur despite the technique employed.

Table 37.2 Drug treatment of dyslipidemias

Drug class	Mechanism of action	Effect on lipids	Major adverse effects
Statins	Competitively inhibit HMG-CoA reductase	LDL ↓	Hepatic toxicity
Atorvastatin		Triglycerides ↓	Muscle toxicity
Fluvastatin		HDL ↑	
Lovastatin			
Pravastatin			
Rosuvastatin			
Simvastatin			
Fibrates	Inhibit hepatic synthesis of VLDL	LDL ↓	Muscle toxicity
Bezafibrate		Triglycerides ↓	
Ciprofibrate		HDL ↑	
Fenofibrate			
Gemfibrozil			
Nicotinic acid	Inhibits hepatic synthesis of VLDL	LDL ↓	Flushing
		Triglycerides ↓	
	Increased activity of lipoprotein lipase	HDL ↑	
Bile acid sequestrants	Inhibit intestinal reabsorption of bile acids	LDL ↓	Gastrointestinal discomfort
Cholestyramine		Triglycerides ↑	
Ezetimib	Inhibits cholesterol absorption in the intestine	LDL ↓	Gastrointestinal discomfort

LDL low-density lipoprotein, *HDL* high-density lipoprotein *VLDL* very-low-density lipoprotein

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Dermatosis and Nutritional Disorders

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Key Points

- *Acne*: A low glycemic-load diet can be recommended to patients. The link between milk and acne needs more research before being recommended to acne patients
- *Atopic dermatitis*: Excessively restrictive diets, especially in atopic children, have led to weight loss, poor growth, calcium deficiency, hypovitaminosis, and kwashiorkor
- *Hair disorders*: Caloric deprivation or deficiency of several components, such as proteins, minerals, essential fatty acids, and vitamins can lead to structural abnormalities, pigmentation changes, or hair loss. Combined deficiencies are not uncommon

- *Nail disorders*: A healthy, well-balanced diet composed of an adequate daily intake of vitamins and minerals facilitates nail health in general. The use of biotin has recently shown promise in treating human nail diseases, especially nail brittleness
- *Skin cancer*: A specific diet should not be recommended for skin cancer prevention, because studies have presented conflicting results
- *Vitiligo*: While there may be a relationship between nutritional elements and vitiligo, further research is needed to elucidate the nature of the association and the clinical application

Acanthosis Nigricans

Nutritional Correlation

Obesity is closely associated with acanthosis nigricans, and more than half of adults who weigh 200% more than their ideal body weight have lesions consistent with acanthosis nigricans. Although it is not universally the case, this dermatosis is weight dependent, and insulin resistance is often present in such patients

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[1, 2]. Obesity-associated acanthosis nigricans may be a marker for higher insulin needs in obese women with gestational diabetes and has been shown to be a reliable early marker for metabolic syndrome in pediatric patients. The lesions may completely regress with weight reduction [1–4].

Skin Manifestations

Acanthosis nigricans is characterized by symmetric, hyperpigmented, velvety plaques that may occur in almost any location but most commonly appear on the intertriginous areas of the axilla, groin, and posterior neck. The posterior neck is the most commonly affected site in children. Acrochordons are often found in and around the affected areas [3, 4].

Complementary Examinations

The vast majority of cases are due to obesity and/or insulin resistance. Screening for diabetes with a glycosylated hemoglobin level or glucose tolerance test is recommended. Screening for insulin resistance with a plasma insulin level is the most sensitive test to detect a metabolic abnormality of this kind because many younger patients do not yet have overt diabetes mellitus and an abnormal glycosylated hemoglobin level, although they do have a high plasma insulin level.

Therapeutic Approach

No treatment of choice exists for acanthosis nigricans. The lesions are treated for cosmetic reasons only. Correction of hyperinsulinemia often reduces the burden of hyperkeratotic lesions. Likewise, in obesity-associated acanthosis nigricans, weight reduction may result in resolution of the dermatosis. Topical medications that have been effective in some cases of acanthosis nigricans include keratolytics (e.g., topical tretinoin 0.05%, ammonium lactate 12% cream) and triple-combination depigmenting cream (tretinoin 0.05%, hydroquinone 4%, fluocinolone acetonide 0.01%) nightly with daily sunscreen. Calcipotriol, podophyllin, urea, adapalene, and salicylic acid also have been reported, with variable results. Oral agents that have shown some benefit include etretinate, isotretinoin, metformin, and dietary fish oils [1, 3, 4].

Acne

Nutritional Correlation

Many patients believe that diet contributes to acne. Diet as a potential treatment for acne is not new, although over the past 100 years the literature examining diet and acne has been inconclusive. Dermatologists have recently revisited the idea and become increasingly interested in the role of medical nutrition therapy in acne treatment [5]. Research has substantiated the role of specific foods, such as dairy products, particularly milk and its derivatives, as well as dietary patterns, including the high glycemic load typical of the Western diet [6]. The evidence is more convincing for high-glycemic-load diets compared with other dietary factors. To date, no randomized controlled trials (RCTs) have investigated the relationship between frequent dairy or milk consumption and acne [5–7].

A high-glycemic-load diet leads to hyperinsulinemia, which initiates a signaling cascade resulting in increased insulin and insulin-like growth factor 1 (IGF-1) activity and decreased IGF-binding protein 3 (IGFBP-3) activity. IGF-1 is known to stimulate key factors of acne pathogenesis, including keratinocyte proliferation,

sebocyte proliferation, and lipogenesis. Milk consumption results in a significant increase in insulin and IGF-1 serum levels comparable with high glycemic food [5–8].

Interventional studies have investigated the effect of low versus high glycemic-load diets on acne. These studies provide compelling evidence that a low-glycemic diet improves acne. Weight loss, however, is a confounding factor [7]. Posterior histopathologic examination revealed reduced sebaceous gland size and decreased expression of sterol regulatory element binding protein 1, a regulator of lipid synthesis, and interleukin-8, an inflammatory cytokine, with a low glycemic diet [9].

Some studies have investigated the association between acne and milk consumption. Acne was positively associated with the frequent consumption of whole milk and skim milk in women and with total, whole, low-fat, and skim milk consumption in girls. In boys, self-reported acne was positively associated with skim milk intake alone [5–7]. Finally, a recent case series reported acne in male patients that was precipitated by whey protein supplementation. These patients experienced resolution of their acne after discontinuing whey protein supplementation [10].

Consumption of salty foods was significantly higher among patients with acne compared with acne-free subjects, making the consumption of salty food a possible participating factor in the development of acne [11].

Some low-quality evidence suggests that tea tree oil and bee venom may reduce total skin lesions in acne vulgaris [12].

Skin Manifestations

Noninflammatory acne is characterized by open and closed comedones. Inflammatory acne originates with comedo formation but then expands to form papules, nodules, and cysts of varying severity (Fig. 38.1) [6, 7].

Fig. 38.1 Inflammatory acne (Courtesy of Dermatology Service of UFCSPA)

Eruptive acneiform lesions can be seen in drug-induced acne and when it is related to diet. Clinically it is an abrupt and monomorphous eruption of inflammatory papules, in contrast to the heterogeneous morphology of lesions seen in acne vulgaris [6, 7, 13].

Complementary Examinations

Related to nutritional features, no complementary examinations are necessary.

Therapeutic Approach

Currently the best dietary approach is to address each acne patient individually, while carefully considering the possibility of dietary counseling [13]. Multiple studies have shown the benefit of a low-glycemic-load diet in treating acne, which therefore can be recommended to patients. While observational studies support the link between milk and acne, more research is required before milk-restricted diets can be recommended to acne patients [6, 7, 13].

Acrodermatitis Enteropathica and Zinc Deficiency

Nutritional Correlation

Zinc deficiency is an uncommon nutritional deficiency that can be inherited or acquired. Acrodermatitis enteropathica (AE) classically refers to the inborn error of zinc metabolism that is inherited as an autosomal recessive disorder. Acquired zinc deficiency is more prevalent and may present in the same fashion [14, 15]. Acquired zinc deficiency may be due to inadequate intake, malabsorption, excessive loss, or a combination of these factors. Transient, symptomatic zinc deficiency has been reported in breastfed, low-birth-weight, and premature infants [14, 16–18] (Chart 38.1).

Certain medical conditions and medications can be predisposing factors for zinc deficiency. Some of these medical conditions include cirrhosis, diabetes mellitus, burns, end-stage renal disease, celiac disease, inflammatory bowel disease, and cystic fibrosis [17–19].

Chart 38.1 Correlation of nutrient deficiency and its cutaneous repercussions

Nutrient	Cutaneous repercussion
Biotin	Alopecia, glossitis, keratosis pilaris, periorificial dermatitis, seborrheic dermatitis, and erythroderma
Copper	Depigmented and thinning hair, alopecia, delayed wound healing
Iron	Pallor, koilonychia, glossitis, alopecia
Selenium	Delayed wound healing, psoriasis, skin cancer
Vitamin A or retinol	Xeroderma, acne, brittle hair, and keratotic follicular papules most commonly in the anterolateral surface of thighs and arms, which may spread to the extensor areas of the upper and lower limbs, shoulders, abdomen, dorsal region, buttocks, and neck; phrynoderma
Vitamin B2 or riboflavin	Mucositis, lip and angular cheilitis, glossitis, xerosis, seborrheic dermatitis, scrotal and vulvar eczema, erythroderma, and toxic epidermal necrolysis
Vitamin B3 or niacin	Pellagra, photosensitive dermatitis in symmetric areas, cheilitis, glossitis
Vitamin B5 or pantothenic acid	Purpura, leukotrichia, seborrheic dermatitis, angular stomatitis, glossitis, and burning feet syndrome
Vitamin B6 or pyridoxine	Seborrheic dermatitis, glossitis, oral mucosa ulceration, lip and angular cheilitis, photosensitive pellagra-like lesions
Vitamin B9 or folic acid and B12 or cobalamin	Lip or angular cheilitis; Hunter's glossitis; diffuse, symmetric hair; and mucocutaneous hypo-and hyperpigmentation
Vitamin C or ascorbic acid	Poor wound healing, keratosis pilaris, perifollicular petechiae, ecchymosis, purpura, brittle hair, scurvy (gingivitis, bleeding gums, keratosis pilaris), Sjögren-like syndrome
Vitamin D	Atopic dermatitis, psoriasis, skin infections, acne, autoimmune cutaneous diseases, and skin cancer
Vitamin E	Atopic dermatitis, acne
Vitamin K	Purpura, petechiae, ecchymosis, hematoma
Zinc*	Acrodermatitis enteropathica (alopecia; acral and periorificial symmetric, erosive and eczematous rash); dry, brittle, and thinning hair; delayed wound healing; paronychia; stomatitis; psoriasiform dermatitis; blepharitis; angular cheilitis; vitiligo-like lesions
Protein	Aged appearance; erythematous or hypopigmented lesions most evident in flexure areas; hyperchromic lesions with smooth, fissured, or erosive surface; brittle, slow growing nails; onychomadesis; follicular hyperkeratosis; pale extremities accompanied by edema; dry, brittle, dull, and thin hair, with brownish-red color before becoming grayish-white, flag signal with alternating dark and light stripes in the hair; angular cheilitis; xerophthalmia; stomatitis; vulvovaginitis

*Reference [14]

Skin Manifestations

In AE the main manifestation is erythematous, vesiculobullous, or pustular lesions that lead to dry, scaly, or eczematous lesions distributed around periorificial and acral areas of the body. The borders of affected areas are sharply demarcated with accentuated, craquelé-like scaling and occasional paronychia. Other symptoms are diarrhea, behavioral changes, and neurologic disturbances. In older children, zinc deficiency is characterized by failure to thrive, anorexia, alopecia, nail dystrophy, and repeated infections [18, 19].

Acquired zinc deficiency can have milder clinical features characterized by eczematous or psoriasiform dermatitis accompanied by perlèche. Areas of pressure or rubbing may also be involved. Some plaques appear annular or nummular and may not be as inflamed in chronically undiagnosed patients. Such lesions may become secondarily infected with *Staphylococcus aureus* or *Candida albicans* [14, 18, 19].

Complementary Examinations

Plasma zinc levels should be tested. Specimens should be collected in plastic syringes or acid-washed Vacutainer tubes with no rubber stopper to prevent exogenous contamination that could lead to spuriously normal measurements. Plasma zinc concentrations less than 50 µg/dL are suggestive, but not diagnostic, of AE. Hair, saliva, or urine zinc levels can be obtained but are rarely needed. Because alkaline phosphatase is a zinc-dependent enzyme, reduced serum levels of alkaline phosphatase in the context of normal zinc levels can indicate a zinc deficiency. However, alkaline phosphatase levels are typically not decreased unless the individual has advanced disease. Analysis of maternal breast milk zinc concentrations may help in differentiating AE from acquired zinc deficiency.

Therapeutic Approach

If treated early, most of the symptoms are reversible and usually cause no sequelae. Treatment of AE requires lifelong zinc supplementation, which typically consists of 1–3 mg/kg of zinc gluconate or sulfate administered orally each day. Clinical response is observed within 5–10 days. Serum zinc levels and alkaline phosphatase values should be monitored every 3–6 months [14, 17–19] (Chart 38.2).

Chart 38.2 Correlation of nutrient deficiency and recommended treatment*

Nutrient	
Biotin	Biotin, 10 mg/day orally
Copper	Elemental copper, 0.1–0.5 g, intravenously, 2×/week
Iron	Ferrous sulfate, 500 mg/day orally
Selenium	Sodium selenite, 200 mg/day orally
Vitamin A or retinol	Vitamin A, 50,000–200,000 IU/day orally
Vitamin B2 or riboflavin	Vitamin B2, 10–20 mg/day orally
Vitamin B3 or niacin	Nicotinic acid, 500 mg/day orally
Vitamin B5 or pantothenic acid	Pantothenic acid, 10 g/day orally
Vitamin B6 or pyridoxine	Pyridoxine, 100 mg/day orally
Vitamin B9 or folic acid and B12 or cobalamin	Folic acid, 1–20 mg/day orally Vitamin B12 of 1mg/weekly parenteral
Vitamin C or ascorbic acid	Vitamin C, 500 mg to 1g/day orally
Vitamin D	Vitamin D, 600–800 IU/day orally
Vitamin E	Vitamin E, 400–800 mg/day orally
Vitamin K	Vitamin K, 1–3mg/single dose intramuscularly
Zinc	Zinc, 15–30 mg/day orally
Protein	1.5 g protein/kg orally

*Reference [14]

Allergic Contact Dermatitis

Nutritional Correlation

Approximately 30–50% of individuals who are allergic to natural rubber latex show an associated hypersensitivity to some plant-derived foods, especially fresh fruits. This association of latex allergy and plant-derived food allergy is called latex-fruit syndrome. An increasing number of plant sources, such as avocado, banana, chestnut, kiwi, peach, tomato, potato, bell pepper, and, recently, turnip, zucchini, and cassava, have been associated with this syndrome. The prevailing hypothesis is that allergen cross-reactivity is due to immunoglobulin E (IgE) antibodies that recognize structurally similar epitopes on different proteins. Some forms of eczema will therefore respond to dietary restriction of certain foodstuffs [20–23].

The oral intake of nickel can induce systemic contact dermatitis in nickel-sensitive individuals and depends on the composition of the diet and on factors such as the food preparation process, whether the food is fresh or canned, and/or whether contamination occurred during processing or through kitchen utensils. Food, water, and cooking utensils are all sources of nickel in the diet. Certain foods, such as cocoa and chocolate, soya beans, oatmeal, almonds and other nuts, and fresh and dried legumes are routinely high in nickel content [20, 24].

Food items most commonly mentioned by patients as aggravating dermatitis due to balsam of Peru are wine, candy, chocolate, cinnamon, curry, citrus fruit, tomatoes, and flavorings [20, 24].

Skin Manifestations

A flare-up of a recurrent erythema and vesicular eczema is the most common clinical manifestation [24].

Complementary Examinations

Patch testing is required to identify the external chemicals to which the person is allergic. The greatest quality-of-life benefits from patch testing occur in patients with recurrent or chronic allergic contact dermatitis. Patch testing is cost-effective and reduces the cost of therapy in patients with severe allergic contact dermatitis.

Therapeutic Approach

Therapy involves avoiding any foods suspected of causing contact dermatitis [20].

Atopic Dermatitis

Nutritional Correlation

Food Allergy

Some controversy exists regarding the role of food antigens in the pathogenesis of atopic dermatitis (AD), in relation to both the prevention of AD and the efficacy of withdrawing foods from the diets of persons with established AD. Most reported studies contain methodological flaws. Because of the controversy surrounding the role of food in AD, most physicians do not remove food from the diet. Nevertheless, acute food reactions (urticaria and anaphylaxis) are commonly encountered in children with AD [7, 25].

The National Institute of Allergy and Infectious Diseases Food Allergy Expert Panel suggests consideration of limited food allergy testing (i.e., cow's milk, eggs, wheat, soy, and peanut) if a 5-year-old child has moderate to severe AD and the following: persistent disease despite optimized management and topical therapy, a reliable history of an immediate allergic reaction after ingestion of a specific food, or both. While food allergy is less common in older age groups, when suspected, the choice of food for testing should be made according to the clinical history and to the most prevalent allergies in a given population. Tree nuts, shellfish, and fish become relevant in subsequent childhood years. In older children, adolescents, and adults, pollen-related food allergy should be taken into account; for example, those with

birch pollen allergy may develop itching in their mouth with exposure to apples, celery, carrots, and hazelnuts [7, 26].

Prebiotics and Probiotics

The role of prebiotics and probiotics in the diet of patients with AD is controversial. The composition of intestinal bacteria is postulated to affect food sensitization in the gastrointestinal tract and AD pathogenesis [7, 27].

Prebiotics are nondigestible food components, commonly oligosaccharides. There is currently insufficient evidence to determine the role of prebiotic supplementation of infant formula for the prevention of allergic disease and food hypersensitivity. Trials are needed to determine whether this finding persists over a longer period of time, applies to other manifestations of allergic disease, is associated with reductions in allergen sensitization, and is reproducible [7, 27].

Probiotics are live microorganisms currently defined as food supplements with established beneficial effect on human health. More studies of probiotic supplementation have been conducted with *Lactobacillus acidophilus*, *L. rhamnosus*, *L. reuteri*, and *L. fermentum* [7, 29].

The aims of intervention are to avert deviant microbe development, strengthen the immature or impaired gut barrier function, and alleviate abnormal immune responsiveness. However, a recent Cochrane Intervention Review suggests that probiotics are not an effective treatment for eczema and may, in fact, carry a small risk of adverse events such as infections and bowel ischemia [30].

Maternal Diet and Breastfeeding

Maternal diets with the goal of avoiding allergens during pregnancy or lactation do not prevent AD. However, exclusive breastfeeding for 4 months or breastfeeding supplemented with hydrolyzed formula is protective against AD in high-risk infants. For infants at normal risk, breastfeeding does not affect the incidence of AD. It has been reported that restriction of maternal diet during pregnancy and lactation does not affect subsequent AD development. Exclusive breastfeeding for 4 months in high-

risk infants was reported to be protective against AD [7, 27].

Vitamins

Recently, reports in the literature have emphasized the impact of vitamin D on the pathogenesis of AD. Considering the immunologic mechanisms involved in AD pathogenesis, vitamin D may influence that process through its immunomodulatory properties. It is known that the active form of vitamin D ($1,25(OH)_2D_3$) increases the expression of antibacterial peptide, thus preventing cutaneous infections. Some studies have demonstrated the link between vitamin D and Toll-like receptors, cathelicidin production, and the increased susceptibility to bacterial infections. In addition, vitamin D stimulates the synthesis of proteins such as filaggrin, which is essential to the formation of the stratum corneum. Thus, vitamin D deficiency may exacerbate AD by altering the skin barrier and undermining the immune system, leading to a subsequent increase in the risk of infections [7, 14, 31] (Chart 38.1).

Studies have looked at the combination of vitamin D plus vitamin E compared with placebo and found significant improvement in AD, suggesting a potential role for dual therapy. At present, although there is some evidence to suggest the use of vitamin E in AD, more studies are needed to confirm this benefit as well as its value in combination with other vitamins [7, 27, 31].

Skin Manifestations

A number of criteria are commonly used for the diagnosis of AD, namely, eczematous changes that vary with age, chronic and relapsing course, early age of onset, pruritus and xerosis.

Complementary Examinations

Diagnosis of an IgE-mediated food allergy relies on a combination of medical history, skin prick testing (SPT), serum IgE testing, and oral food challenges. Classically, neither the skin prick test nor allergen-specific serum IgE testing is

diagnostic because of their limited positive predictive value for clinical allergy [26].

Tests often performed for evaluation include SPT and serum-specific IgE level determination, which assess for immediate/type I hypersensitivity reactions. In cases of extensive eczematous lesions, severe dermatographism, or the recent use of oral antihistamines, specific IgE (sIgE) measurement may be preferable over SPT. With both tests, the negative predictive value is high (95%) and the specificity and positive predictive value are low (40–60%). Negative test results are helpful to rule out food allergy, but positive results only signify sensitization, and require clinical correlation and confirmation to establish the presence of allergic disease and the exact type of allergic response [7, 26].

Baseline sIgE values for cow's milk, peanut, egg white, and seafood have been associated with an increased risk of developing allergies to these foods, while wheat and soybean sIgE levels have not. Higher specific IgE levels and larger wheal sizes (8–10 mm) are associated with a greater likelihood of reaction on challenge. Measuring total serum IgE levels alone, or comparing with allergen-specific levels, is not helpful in determining food allergy [7].

In recent years, atopy patch tests (APTs) have been introduced to assess for type IV hypersensitivity/eczematous reactions. Food APTs are not commonly used in the evaluation of patients. These conflicting findings might be explained by the sometimes difficult interpretation of APTs because of nonspecific reactions. In addition, while AD patients are more reactive than healthy controls, the results do not necessarily correlate with disease severity or clinical outcome, and APTs are therefore not currently recommended for routine use [7].

Therapeutic Approach

Food Elimination/Avoidance Diets
A Cochrane review of food allergy in patients with AD showed that an egg- and milk-free diet provided no apparent benefit in unselected participants with atopic eczema. There appears to be little benefit in eliminating cow's milk from the diet or using an "elemental" (liquid diet containing only amino acids, carbohydrates, fat, minerals, and vitamins) or "few foods diet" for improving atopic eczema in people who have not undergone any form of testing (for specific IgE to food allergens). There may be some benefit in using an egg-free diet in infants with suspected egg allergy who have positive specific IgE to eggs. This is important, particularly since some children with AD show impaired physical development, secondary to gastrointestinal involvement. Although strict elimination diets may be impractical, there is evidence to show that a strict antigen avoidance regimen may be associated with improvement of refractory widespread AD when conventional treatments have failed [7, 20, 26].

Excessively restrictive diets, especially in atopic children, have led to weight loss, poor growth, calcium deficiency, hypovitaminosis, and kwashiorkor. Proper medical supervision, nutritional counseling from a dietician, and supplementation should be included if elimination/avoidance diets are pursued for a prolonged period. Even in those individuals with clinically relevant food allergy, avoidance diets are generally helpful to avoid the effects of IgE-mediated/immediate reactions but are unlikely to affect the course of AD [7, 20].

Prebiotics and Probiotics
Prebiotics are found in vegetables (artichoke, asparagus, bananas, garlic, leeks, onion, tomatoes), grains (barley, rye, whole grains), roots (chicory root, dandelion root, elecampane root), fermented dairy products (e.g., yogurt, buttermilk, kefir), naturally in breast milk, and in some products with added prebiotics (e.g., bread, breakfast cereals, sauces and soups, and dairy products such as yoghurt). Probiotics are mainly found in some yoghurts and can also be consumed as capsules, tablets, beverages, and powders [7, 20, 29].

Maternal Diet During Pregnancy and Lactation
The evidence from studies into the role of dietary restriction during pregnancy and lactation has been conflicting. A Cochrane review examining

four trials involving egg and cow's milk restriction during pregnancy showed no significant difference in the incidence of AD. Definite conclusions about the effect of breastfeeding in either preventing or delaying the onset of AD are difficult to make. Studies suggest that exclusive breastfeeding for 3–4 months may be beneficial in preventing AD in mothers of infants with a family history of atopy [7, 20, 30].

Vitamins

The specific treatment of vitamin deficiency depends on each case. The general posology is vitamin E, 400–800 mg/day orally and vitamin D, 600–800 IU/day orally for 60 days [14, 31, 32] (Table 38.1).

Autoimmune Cutaneous Diseases

Nutritional Correlation

Eating Disorders

Eating disorders (EDs), including anorexia nervosa and bulimia nervosa, are often associated with autoimmune disease. This fact supports the hypothesis of comorbidity of these disorders and suggests that immune-mediated mechanisms could play a role in the development of EDs. The studies suggest that the link between these facts is based on shared immunologic mechanisms rather than on the shared genetic background, e.g., the shared human leukocyte antigen risk genotype. EDs with correlated cutaneous manifestations include Sjögren's syndrome (SS), scleroderma, sarcoidosis, pemphigus, dermatitis herpetiformis (DH), psoriasis, vitiligo, lupus erythematosus, dermatomyositis, mixed connective tissue disease, and idiopathic thrombocytopenic purpura [33, 35, 36].

Vitamin D

Vitamin D deficiency is clearly correlated with autoimmune cutaneous disease. A high prevalence of vitamin D deficiency was noted among patients with autoimmune diseases, especially systemic lupus erythematosus (SLE). These observations led to the hypothesis that vitamin D deficiency may exacerbate autoimmune conditions. Similarly, patients with SS and scleroderma

tend to have very low vitamin D levels. This may be attributed to characteristics of the diseases, including disseminated skin involvement and renal injury that may interfere with vitamin D synthesis, as well as vitamin D malabsorption in cases of advanced intestinal disease. Moreover, patients with SLE and SS related to severe vitamin D deficiency demonstrated a more severe disease course [14, 34] (Chart 38.1).

Complementary Examinations

Standard laboratory studies that are diagnostically useful when autoimmune cutaneous diseases is suspected should include the following: complete blood count with differential, serum creatinine, urinalysis, erythrocyte sedimentation rate or C-reactive protein, complement levels, liver function tests, creatine kinase assay, spot protein/spot creatinine ratio, antinuclear antibody, anti-dsDNA, anti-Sm, anti-SSA (Ro), or anti-SSB (La).

Serum 25(OH)D is the best test to determine vitamin D status. The circulating half-life of 25(OH)D is 2 weeks. A 25(OH)D level of less than 30 ng/mL is considered vitamin D insufficient. A 25(OH)D level of less than 15 or 20 ng/mL has been used to define vitamin D deficiency. Intestinal calcium absorption is optimized at levels above 30–32 ng/mL. Parathyroid hormone levels start to rise at 25(OH)D levels below 31 ng/mL, which is another marker of vitamin D insufficiency.

Therapeutic Approach

Eating Disorders

It is important to remember the correlation between nutritional and autoimmune diseases when selecting the most appropriate approach and treatment for the patient. In such cases, a multidisciplinary team (e.g., dermatologists, psychiatrists) should treat the patient [33].

Vitamin D

The specific treatment of vitamin deficiency depends on each case. The general posology is vitamin D, 600–800 IU/day orally for 60 days [14, 34] (Table 38.1).

Bullous Diseases

Nutritional Correlation

A variety of dietary factors have been proposed to play a role in the pathogenesis, exacerbation, and therapy of autoimmune and nonautoimmune bullous skin diseases, although in DH the role of food components (gluten) is well established [20, 38].

Pemphigus

A variety of substances (tannins, thiols, phenols, isothiocyanates, phycocyanins) in different foods are believed to have an effect in the induction, maintenance, and exacerbation of pemphigus (including pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, and IgA pemphigus), in genetically predisposed individuals. The basis for that belief is the similarity of their chemical structure to that of drugs known to induce the disease. In addition, environmental factors such as the high tannin content in water is believed to play a role in endemic pemphigus among populations in Amazonian Brazil (fogo selvagem) and India. A list of foods containing these substances includes garlic, leek, chives, onion, mustard (thiols), black pepper, red chilies, mango, pistachio, cashews, aspartame, food additives (phenols), mango, cassava, yucca, guarana, betel nuts, raspberry, cranberry, blackberry, avocado, peach, ginger, ginseng, tea, red wine, coffee, spices, eggplant (tannins), mustard, horseradish, kale, cauliflower (isothiocyanates), and *Spirulina platensis* alga (phycocyanins). In some case reports, exclusion of these foods from the diet resulted in disease cessation or improvement, while challenge with the foods caused recurrence. No case reports of pemphigus induced by isothiocyanates have been reported to date, although they are believed to be similar to thiol-containing compounds [20, 28, 37]. The thiol allyl compounds and/or tannins may either be incorporated into keratinocytes, thus leading to simple biochemical acantholysis, or may release sequestered desmoglein antigens from immunologically privileged sites and also interfere with the immune balance, thus leading to antibody-mediated immunologic acantholysis. As occurs with thiol-based drugs, a combined mechanism is also possible [37]. Antigliadin antibodies have been reported in some pemphigus patients. In a recent case report, two patients with new-onset pemphigus were started on a gluten-free diet with subsequent complete remission of the disease. Both patients had serologic markers of gluten-sensitive enteropathy, without signs of celiac disease [20, 28, 38].

Bullous Pemphigoid

No dietary factors have been implicated in the induction of bullous pemphigoid. There is only one case report of nickel-free diet associated with cessation of dyshidrosiform pemphigoid [20, 38, 39]. The presence of antigliadin antibodies in the sera of bullous pemphigoid patients may indicate that some of them have gluten sensitivity. There have been no reports, however, of bullous pemphigoid improving with a gluten-free diet [39].

Linear IgA Disease

In some case reports, gluten restriction in the presence of an underlying gluten-sensitive enteropathy resulted in resolution of linear IgA disease, with recurrence when gluten was reintroduced [20, 38].

Dermatitis Herpetiformis

Research into DH, especially the elucidation of its pathogenesis, has shown that it is not simply a bullous cutaneous disease but a cutaneous-intestinal disorder caused by gluten hypersensitivity. Its association with celiac disease is well established. Exposure to gluten remains the trigger of an, as yet partially elucidated, inflammatory cascade [20, 28, 40].

A gluten-free diet has been shown to result in resolution of enteropathy, a decrease in or the absence of the need for medication, protective effects against the development of lymphoma, and a general feeling of well-being [20]. Gluten is an amorphous protein composed of gliadin and glutenin amino acids, which are found in cereal seeds from the Gramineae family, such as wheat, barley, oats, malt, and rye. They are cereals that contain starch, lipids, and proteins (gliadin, glutenin,

albumin, and globulin). Specifically, wheat protein is composed of 68% gliadin and 32% glutamine, and is therefore commonly referred to as wheat gluten. Examples of food products that contain this protein are flour, chocolate milk, which contains malt, processed cheese, beer, whiskey, vodka, mustard, ketchup, mayonnaise, and salami [41]. Recently, it has been hypothesized that patients with DH may be better able to tolerate oats, because of their lower protamine content compared with other cereals. Inclusion of oats in gluten-free diets remains controversial. Because some oats and oat-containing products may be contaminated with gluten-containing cereals, care must be taken when introducing oats into a gluten-free diet [20, 28, 38].

Dietary factors other than gluten may be important in the pathogenesis of DH. Most of the antigens that lead to immune responses are believed to be full-length proteins. Therefore, an elemental diet that contains only amino acids, not full-length proteins, could be beneficial in DH patients because, theoretically, no antigenic stimulation would take place. Disease remission with the elemental diet, as reported in various studies, supports the concept that other antigens may be involved in the pathogenesis of DH [20, 38].

There are two case reports of milk consumption affecting the course of DH, suggesting that milk proteins may serve as DH antigens. A DH patient who was started on a gluten-free diet did not improve until milk and milk proteins were excluded [20, 38].

The symptoms and signs of DH may be exacerbated by topical or oral administration of potassium iodide. When iodides were applied to the healthy skin of DH patients in a potassium iodide patch test study, vesicles appeared that were histologically identical to DH lesions. Potassium iodide and iodine-containing foods (including seafood), as well as thyroid disorders (treated or not treated with iodine), have also been associated with DH onset or flares [20, 38].

Epidermolysis Bullosa

Epidermolysis bullosa patients, especially those with junctional and recessive dystrophic subtypes of the disease, are at significant risk of nutritional compromise. Nutritional profiles of the patients consistently show malnutrition and growth stunting resulting from oral, esophageal, and oropharyngeal problems, such as oral blistering and ulcerations, abnormal esophageal motility, esophageal strictures, dysphagia, dental problems, digestion and absorption problems, anal erosions, fissures, and rectal strictures resulting in chronic constipation, loss of blood and protein through open skin blisters, and hypermetabolism resulting in increased heat loss and protein turnover. Vitamin and mineral deficiencies are common in these patients, particularly iron deficiency, and a refractory anemia that is unresponsive to oral supplements may develop. As with iron, other elements such as zinc, selenium, vitamin E, and carnitine may be deficient. Vitamin D deficiency and lack of physical exercise are two factors that have deleterious effects on bone health, and put patients at risk for low bone mass and fragility fractures [20, 38].

Skin Manifestations

Bullous diseases present typical signs and symptoms, although dietary factors play a role in their pathogenesis or exacerbation. Figure 38.2 shows DH lesions.

Fig. 38.2 DH lesions: papules, vesicles, erosions, and crusts (Courtesy of Dermatology Service of UFCSPA)

Complementary Examinations

Patients with DH may have malabsorption and nutritional deficiencies of iron, folic acid, selenium, and vitamin B12 as result of inflammation in the intestinal mucosa. Therefore, laboratory tests should be performed regularly to check the nutritional status of such patients. Exclusion of celiac disease is mandatory. IgA anti-tissue transglutaminase antibody is the preferred single test for detection of celiac disease in individuals over the age of 2 years [20, 28, 38].

Epidermolysis bullosa patients are at significant risk of nutritional compromise. The following profiles should be carried out: iron, ferritin, zinc, selenium, vitamin E, and vitamin D (25(OH) D) [20, 38].

Therapeutic Approach

Dietary recommendations should not be overlooked in bullous diseases, and additional studies regarding dietary manipulation and the effect of dietary components are required to better understand the condition and treat patients [20, 38].

Patients with pemphigus should be advised to maintain a balanced diet and avoid foods spiced with garlic, onion, and leek as these culinary plants, belonging to the genus Allium, contain thiol allyl compounds with a proven acantholytic potential. Patients should also be warned against the ingestion of very hot foods and beverages in view of the possible acantholytic effect that the excessive heat may exert on oral and esophageal mucosae. Milk is a nutrient to recommend, because of its high protein content, its easy intake even in the presence of painful oral erosions, and its high level of an oxidative enzyme (sulfhydryl oxidase) that has the potential to neutralize the acantholytic effect of thiol allyl derivatives found in the vegetarian diet [20, 37, 38].

A gluten-free diet is essential in the treatment of patients with DH, since cutaneous and intestinal clinical manifestations are gluten dependent and improve with suspension of its intake. Dapsone remains the primary drug for treatment, but requires monitoring because of its possible side effects, some of which are potentially lethal

[28, 40]. The average duration of the gluten-free diet to reduce or discontinue dapsone is 18 months. A long-term gluten-free diet has also been shown to decrease the intensity of skin IgA fluorescence [20, 38].

To date, no clinical trials of iodide-free diets have been carried out in DH patients. Such diets could be considered in patients who consume large amounts of iodide-containing foods (salt, fish) or who do not respond to a gluten-free diet [20, 38].

Depending on their vitamin status, appropriate vitamin supplementation should be given to epidermolysis bullosa patients to optimize their nutrition. Vitamin D and calcium supplementation should be given to young patients in particular in an effort to prevent negative consequences to bone health. Nutritional support is an essential part of long-term management and improves the quality of life by accelerating wound healing, reducing infections, and promoting growth and development. The goals of nutritional support are to address the malnutrition and nutrient and vitamin deficiencies, while alleviating the feeding difficulties and complications that affect the nutritional status in these patients. Chronic constipation frequently contributes to malnutrition and growth failure. A high-fiber diet and adequate fluid intake are important to ease the passage of stools. In infants with epidermolysis bullosa, breast milk is recommended, complemented or replaced by a specially designed formula in cases of poor weight gain. In older children, food texture and consistency should be modified to match individual tolerance [38].

A few case reports have suggested that vitamin E therapy, especially in large doses, may be beneficial in epidermolysis bullosa patients. The action mechanism of vitamin E is believed to involve the reduction of collagenase activity, which results in decreased blister formation [20, 38].

Energy-Protein Malnutrition

Nutritional Correlation

Energy-protein malnutrition (EPM) can be classified as marasmus, kwashiorkor, and marasmus-kwashiorkor. Marasmus refers to a global and

chronic deficiency of nutrients resulting from lack of food intake or absorption. Kwashiorkor refers to a disproportionately greater absorption or ingestion of carbohydrates compared with fat and protein intake. Marasmus-kwashiorkor is an intermediate state between them. EPM is uncommon in adults, but has been associated with anorexia nervosa and malabsorptive disorders such as Crohn's disease, cystic fibrosis, and postbariatric surgery. In EPM, the skin becomes dry with scaling and cracking. There may be peeling of patches of skin referred to as the flaky paint sign. This peeling leaves behind a raw surface. Hyperpigmented plaques develop in areas exposed to trauma. The hair becomes thin, sparse, and brittle, and falls out easily. It often loses its normal pigmentation, becoming dull brown or reddish-tinged. If periods of inadequate intake are interspersed with periods of good nutrition, when the normal hair color is restored, horizontal stripes develop in the hair, referred to as the flag sign. Nails may be fissured or ridged. There is atrophy of the papillae on the tongue, angular stomatitis, and cheilosis. As malnutrition progresses, the child becomes weak and hypotonic. The infant or child may appear very quiet, apathetic, restless, or irritable. Older children have a limited attention span [14, 42–44] (Chart 38.1).

Skin Manifestations

From a dermatologic viewpoint, the following manifestations can be found: dry, wrinkled skin giving a more aged appearance; erythematous or hypochromic lesions are seen mostly in areas of friction or flexure, which over time become very evident and hyperpigmented, with smooth, fissured or erosive surfaces. Nails are brittle, slow growing, and with areas of onychomadesis. Areas of follicular hyperkeratosis, and pale extremities accompanied by swelling may also occur. The hair may be dry, brittle, dull, thin, with a red-brownish color before becoming grayish-white. The flag sign depicts alternate dark and light bands in the hair. Angular cheilitis, xerophthalmia, stomatitis, and vulvovaginitis may also be seen [43].

Complementary Examinations

Blood glucose, examination of blood smears by microscopy or direct detection testing, hemoglobin, urine examination and culture, stool examination by microscopy for ova and parasites, serum albumin, human immunodeficiency virus (HIV) test, and electrolytes.

Therapeutic Approach

EPM treatment should be individualized according to the type and severity of the presented manifestations. However, it is essential to correct their cause and supplement the deficient macronutrients [14, 42, 43] (Table 38.1).

Hair Disorders

Nutritional Correlation

Hair follicle cells have a high turnover. Their active metabolism requires a good supply of nutrients and energy. Caloric deprivation or deficiency of several components, such as proteins, minerals, essential fatty acids, and vitamins, caused by inborn errors or reduced uptake, can lead to structural abnormalities, pigmentation changes, or hair loss, although exact data are often lacking. Combined deficiencies are not uncommon, especially in malnutrition [28, 36, 45].

Malnutrition and Weight-Loss Diets

Marasmus is a diet low in calories, whereby amino acids are used to provide energy. The glycogen content of the follicular sheath is reduced, providing less energy for cell mitosis [14].

Kwashiorkor is a result of a low protein intake in a calorically normal diet. It is characterized by reddish, short, dull hair and telogen and dystrophic effluvium. Other conditions involving low protein uptake include infants on special diets, such as in urea-cycle disorders, milk-free diets, gastrointestinal disease, blood loss and blood donation, anorexia nervosa, depression, drug addiction, or malignancy. Protein is the major constituent of hair

fibers. Therefore, reduced protein uptake can impair hair growth, even before serum albumin levels are decreased [14, 28].

Diets for weight loss can also lead to hair loss, especially if the daily calorie intake is less than 1,000 kcal and if protein intake is inadequate. Hair loss may be even more profound in diets with a negative nitrogen balance (loss of lean body mass) and be partly due to reduced thyroid activity [45] (Chart 38.1).

Vitamin C

Ascorbic acid is essential for collagen synthesis and crosslinkage of keratin fibers. The reference daily intake for men is 90 mg and for women 75 mg. A deficiency is called scurvy and often occurs in elderly patients, alcoholics, those with mental incapacity, and patients with chronic disease [14, 45].

Zinc

Zinc is a trace element that is required by approximately 300 enzymes, contributing to growth, development, wound healing, immune function, and collagen synthesis, among many other functions. It is essential and must be obtained from the diet. Poor dietary intake of meat and fish can result in deficiency, especially when cereal grains that contain phytate, which chelates zinc and prevents absorption, are a dietary mainstay. Some infant formulas are low in zinc, and in breast milk it is more bioavailable than zinc in formula, culminating with the onset of signs of zinc deficiency, early in life. Zinc may be inadequately absorbed in patients with bowel disease and cystic fibrosis. Increased metabolism or excretion of zinc occurs in a variety of conditions, including alcoholism, malignancy, burns, infections, pregnancy, renal disease, sickle cell disease, collagen vascular disease, and anorexia nervosa. Certain medications, such as diuretics, valproic acid, and penicillamine, can lower zinc levels. The required daily zinc intake for men and pregnant women is 11 mg, and 8 mg for women [14, 28, 45, 46].

Essential Fatty Acids

A deficiency of essential fatty acids can cause changes in hair similar to those seen in zinc deficiency. Essential fatty acid deficiency (EFAD) occurs from decreased intake of linoleic and linolenic acids, long-chain polyunsaturated fatty acids that are important components of the stratum corneum. Linoleic acid is the precursor to arachidonic acid, which in turn is a precursor of prostaglandins, leukotrienes, and thromboxane. EFAD in children is associated with protein-energy malnutrition, low-birth-weight infants, malabsorption, and historically with long-term parenteral nutrition. It may follow surgery in adults [14, 45, 46].

Selenium

Deficiency in selenium, an essential trace element found in soil, can also cause changes in hair similar to those of zinc deficiency. Selenium is a component of at least 35 proteins, many of which are enzymes. An important metabolic system dependent on selenium is glutathione peroxidase, a major antioxidant enzyme. Like EFAD, selenium deficiency can occur in low-birth-weight infants and in patients requiring total parenteral nutrition. It also occurs in locations where the soil selenium content is low [45, 46].

Selenium deficiency has been associated with hair loss after adjuvant chemotherapy with cisplatin. How lack of selenium causes lightening of hair color is unknown. Sulfur-containing compounds such as cysteine and glutathione can shift synthesis of melanin from dark eumelanin to lighter pheomelanin [46].

The reference daily intake for adults is 55 mg. Selenium intoxication from overdosed supplements has been reported [14, 46].

Vitamin A

Vitamin A deficiency is usually discovered in the presence of characteristic ophthalmologic findings, including nyctalopia (night blindness), conjunctival dryness, and, when severe, corneal damage and blindness. Although rare in developed countries, it can occur in patients with malabsorption and in those with EDs. Children are particularly susceptible [45].

Biotin

Biotin (vitamin H) is a cofactor of the carboxylase group of enzymes. These are synthesized as inactive precursors, and become activated when linked to biotin by the enzyme holocarboxylase

synthetase. Biotin deficiency can be genetic or acquired. Because it is present in many types of foods and synthesized by bacteria in the gastrointestinal tract, acquired biotin deficiency is uncommon. An important cause of acquired biotin deficiency in children and adults is the antiseizure medication valproic acid. Biotinidase activity was decreased in these patients and was normal in those treated with lower doses of valproic acid who did not develop hair loss. Biotin deficiency has also been reported in patients with Leiner's disease, which, among other findings, is associated with generalized seborrheic dermatitis and failure to thrive. Acquired biotin deficiency in adults occurs in the setting of malabsorption, alcoholism, pregnancy, and unusual dietary habits. In fact, the most frequent cause of acquired biotin deficiency in adults is excess intake of raw eggs. Eggs contain the protein avidin, which tightly binds biotin and prevents its absorption. Cooking denatures avidin, thus inhibiting biotin binding. The reference daily intake for adults is 30 μg [45, 46].

Iron

Iron deficiency is the most common nutritional deficiency worldwide and is associated with developmental delay, diminished intellectual performance, and decreased resistance to infection. The most severe consequence of iron deficiency is anemia resulting from inadequate intake, impaired absorption or transport, physiologic losses, or chronic blood loss secondary to disease. Iron deficiency can be avoided through proper dietary intake. The heme found in meat, poultry, and fish has a higher availability than the nonheme iron found in plants and iron-fortified food, so vegetarians have a recommended daily allowance that is twice normal. The coconsumption of vitamin C enhances iron absorption, while tannins (found in tea and coffee) and phytates (found in bran, cereal grains, flour, legumes, nuts, and seeds) inhibit iron absorption [14, 28, 45].

The mechanism by which reduced iron stores affect hair loss is unknown. Possible mechanisms include the requirement for iron as a cofactor for ribonucleotide reductase, the rate-limiting enzyme for DNA synthesis, or from inhibition of iron-dependent coenzymes such as stearoyl-coenzyme A desaturase. Hair follicle matrix cells are among the most rapidly dividing cells in the body and may be exquisitely sensitive even to a minor decrease in iron availability, resulting in diminished hair growth in the presence of iron deficiency [45].

Before the development of iron-deficiency anemia, there is a period when iron stores are deficient and hemoglobin levels are normal. Serum ferritin, which is one of the most sensitive and specific markers for iron deficiency, is reduced during this period before the development of anemia. An extensive review revealed that serum ferritin had a greater predictive value than other tests of iron status. Ferritin levels need to be interpreted with caution, because ferritin is an acute-phase reactant and is elevated in inflammatory conditions and chronic disease anemia [28, 45].

Various observational studies on the association between decreased ferritin levels and hair loss have resulted in opposing conclusions. The lack of consensus on the threshold level for iron deficiency and lack of proof that reversing the deficiency reverses the hair loss precludes the statement that iron deficiency is a causative factor in adults with chronic telogen effluvium or diffuse alopecia [28, 45, 46].

The daily reference intake is 8 mg for men and 18 mg for women between 19 and 50 years of age. Different values apply for children, seniors, and pregnant or lactating women [45].

Copper

Copper is crucial for the amine oxidase activity required for oxidation of thiol groups to dithio-crosslinks, which are essential for keratin fiber strength. Some enzymes also depend on copper, such as ascorbic acid oxidase and tyrosinase. In children, a rare autosomal-recessive malabsorption disorder, Menkes kinky hair syndrome (MKHS), may be present. Acquired deficiency is also seen in premature babies, inadequate cow's milk, or parental alimentation, and after prolonged zinc therapy. The reference daily intake for adults is 900 mg [45, 46].

Vitamin D

The role of vitamin D for hair growth is still under investigation. Therefore, obtaining a vitamin D level in telogen effluvium can be helpful. The daily intake for adults is 200–400 IU [45, 46].

Hypervitaminosis

Although excess selenium can cause hair loss, most of what is written about vitamin toxicity causing changes in hair pertains to vitamin A. Hypervitaminosis A is a dangerous condition and can result in liver failure, increased intracranial pressure, and death. The skin is frequently involved in both the acute and chronic forms. Acute vitamin A toxicity is caused by inadvertent consumption of high doses of vitamin A, as was reported in Arctic explorers after a single meal of polar bear or seal liver, or consumption of fish liver. Chronic toxicity results from supplementation exceeding the recommended dose of 5,000 IU daily or inadvertent chronic ingestion [46].

Skin Manifestations

In marasmus the hair is thin, sparse, fragile, and even more easily shed than in kwashiorkor, whereas lanugo body hair may be increased. Children with marasmus appear emaciated and have loss of subcutaneous fat. Alopecia due to telogen effluvium may occur [43, 45, 46].

The cutaneous findings in kwashiorkor are much more apparent. Hair may be brittle and dry, as in marasmus, but may also be soft and fine, with reduced diameter. Hair elasticity is reduced. Eyelashes may be affected, becoming fine and unruly and taking on a broomstick appearance. A characteristic finding in kwashiorkor is lightening of hair color (hypochromotrichia). Sometimes scalp hair exhibits a banded pattern, known as the flag sign. This is due to repigmentation of the shaft during periods of improved nutrition as a result of decreased melanin content in the hair shaft [43, 46].

Hair changes typically seen with vitamin C deficiency include corkscrew hairs, perifollicular hyperkeratosis and hemorrhage, follicular plugging, and curling. These findings are most noticeable on the forearms, abdomen, and legs. Corkscrew hairs are coiled or looped hairs, mainly on the arms, trunk, and legs. They are caused by a decreased number of reduced disulfide bonds, leading to decreased keratin

Fig. 38.3 Zinc deficiency lesion (Courtesy of Dr. Renan R. Bonamigo)

crosslinkage, and possibly exacerbated by altered perifollicular connective tissue. Perifollicular hemorrhage appears later and is more common on the lower extremities, anterior forearms, and abdomen. The uniform petechial eruption of scurvy can be mistaken for leukocytoclastic vasculitis, but the presence of corkscrew hairs and the perifollicular nature of the purpura are pathognomonic if recognized. Other symptoms include ecchymoses, bleeding gums, chronic wounds, and infections. Children with scurvy do not always develop the classic cutaneous findings seen in adults, although they may present with skin findings, particularly alopecia [46].

Zinc deficiency can lead to telogen effluvium, thin white and brittle hair, as well as nail dystrophy, a seborrheic and, later, eczema-like or psoriasiform acral and perioral dermatitis (Fig. 38.3), cheilitis, blepharoconjunctivitis, infection, and skin superinfection with *C. albicans* and *S. aureus*. Other symptoms are diarrhea, neurologic disturbances, and growth retardation. Histology shows pale superficial epidermal cells and single-cell necrosis [14, 46].

The clinical features of selenium deficiency are similar to those of zinc deficiency. The cutaneous changes typical of selenium deficiency are often delayed, and deficiency can be subclinical for one to several years. The clinical features of selenium deficiency may occur in infants. Alopecia with pseudoalbinism is common at the time of diagnosis of selenium deficiency, and is considered an early clinical sign [46].

With vitamin A deficiency, the characteristic cutaneous manifestation is phrynoderma. This is a follicular hyperkeratosis with keratin plugs on extensor surfaces, similar to keratosis pilaris. Little has been written on the mechanism by which this occurs. Phrynoderma typically spares the hands, feet, and face. Papules and crateriform nodules have been reported [14, 46].

Surviving infants with the genetic form of biotin deficiency have extensive dermatitis and severe alopecia. Terminal and vellus hair follicles may be lacking on the scalp. In addition, eyebrows, eyelashes, and lanugo hairs may be absent or sparse. There are some case reports of AE-like eruptions [46].

Hypopigmented hair and pili torti are typical in MKHS, as well as the degeneration of brain, bones, and connective tissue, including arterial occlusion, and pale and lax skin. It is associated with copper deficiency [46].

Because the symptoms of chronic hypervitaminosis are insidious, skin changes can be a clue to the diagnosis. They include pruritus, diffuse scaling, desquamation, lip fissures, sore tongue and mouth, brittle nails, nail dystrophy, and diffuse alopecia [14, 45, 46].

Complementary Examinations

Depending of the type and cause of hair loss, complementary examinations should be performed.

Related to nutritional features, the following serum tests are necessary: albumin, zinc, selenium, iron, ferritin, and 25(OH)D.

Therapeutic Approach

Patients often ask if there are any vitamins they can take to help their hair grow and look healthy. However, most vitamins and minerals are obtained from a healthy diet, with the possible exception of iron, and most well-nourished patients do not require supplementation. Exceptions to this occur in patients with malabsorption, chronic illness, congenital heart disease, malignancy, neuromuscular disease, EDs, special diets, and in the elderly [45, 46].

Some clinicians suggest biotin replacement for healthy patients with hair loss. However, there are no clinical trials showing the efficacy of biotin in hair loss, and it is not routinely recommended. The dose recommended varies from 2 to 10 mg per day [45–47].

Although traditionally used in nonspecific hair treatments, zinc supplementation has not been proved to have a beneficial effect on hair growth in patients with normal serum zinc levels. During treatment, zinc levels should be monitored because overdose can lead to copper or calcium deficiency, drowsiness, and headache. The recommended dose for adults is 25–50 mg of elemental zinc and 0.5–1 mg/kg for children [14, 46].

The treatment of MKHS consists of infusions with copper salts [46].

Most authors consider a ferritin level of at least 40 mg/L as adequate in their female patients, while others only require 10 mg/L and some require 70 mg/L. To correct iron deficiency, ferrous fumarate, ferrous lactate, ferrous gluconate, or ferrous sulfate should be taken for several weeks in two to three daily doses [14, 28, 46].

Antioxidants may have long-term effects on hair aging, but are difficult to assess. Taurine, an amino acid, has been shown to promote follicle cell survival in vitro, when combined with the polyphenol catechin and other ingredients. L-Carnitine has been shown to stimulate hair follicle cells in vitro. Components derived from soybeans may also have an effect on hair growth through anti-inflammatory and estrogen-dependent mechanisms, but studies in vivo are lacking and an increased dissemination of hemangioma rubi has been reported. Orthosilicic acid increased hair tensile strength and thickness in some small studies. L-Cysteine supplementation has shown a significant effect in the treatment of diffuse telogen effluvium, avoiding the temporary loss of several thousand hairs. Further studies are needed to expand the evidence regarding the effects of nutritional supplements on hair [45].

There is probably a correlation between alopecia areata and vitamin D deficiency, suggesting that vitamin D deficiency might be a significant risk factor for alopecia areata. More studies with larger numbers of patients are needed to confirm this hypothesis [14, 48] (Table 38.1).

Oral Mucosa Disorders

Nutritional Correlation

The oral manifestations of nutritional deficiency include nonspecific signs and symptoms that involve the mucous membranes, the teeth and periodontal tissues, the salivary glands, and the perioral skin. Owing to the rapid rate of cell turnover in the mucous membranes (3–7 days), the oral cavity may exhibit early signs and symptoms of systemic disease or nutritional deficiency [28, 49].

Water-soluble vitamins that involve the oral mucosa include vitamins B2, B3, B6, and B12, folic acid, and vitamin C. Water-soluble vitamins are not stored in the body in large amounts, so they must be supplied to the body by the diet on a frequent or daily basis. Fat-soluble vitamins that affect the mucosa include vitamins A, D, and E. Minerals relevant to the oral mucosa are calcium, fluoride, iron, and zinc [49] (Chart 38.1).

Vitamin B2
Patients with riboflavin deficiency are at risk for developing edema of the pharyngeal and oral mucous membranes, angular cheilitis, stomatitis, and glossitis [49].

Vitamin B3
Deficiency of this vitamin is referred to as pellagra and may manifest as bright red glossitis, burning mouth, gingival erythema, and dental caries [20, 49].

Vitamin B6
Those at high risk of pyridoxine deficiency include alcoholics and patients taking medications that react with B6 such as isoniazid, L-dopa,

penicillamine, and cycloserine. The condition orally presents as glossitis, cheilitis, and gingival erythema [28, 49].

Vitamin B9 (Folic Acid)
Those at high risk of folic acid deficiency include the elderly, alcoholics, and those taking medications that interfere with it, such as methotrexate and phenytoin. Deficiency leads to megaloblastic anemia. Clinical manifestations include burning of the tongue and oral mucosa, a red and swollen tongue, and angular cheilitis [49].

Vitamin B12
The elderly, vegetarians, and those with resected stomach or ileum are particularly susceptible to deficiency of this vitamin. Deficiency of vitamin B12, known as pernicious anemia, presents with megaloblastic anemia, and manifests orally as a red, atrophic, beefy, burning tongue. In addition, vitamin B12 deficiency, along with folic acid and iron deficiencies, is associated with recurrent aphthous stomatitis [14, 49].

Vitamin C (Ascorbic Acid)
Among those at high risk of vitamin C deficiency, also known as scurvy, are alcoholics and individuals with inadequate consumption of fruits or vegetables, the elderly, and infants who consume only cow's milk. Smokers who are deficient in vitamin C are particularly prone to develop periodontal disease. Scurvy presents with hemorrhagic gingivitis with enlarged blue or red gingiva, gingival bleeding, swollen gingiva, and infections. Scurvy also affects dentition, presenting with loose teeth, interdental infarcts, and tooth loss [14, 49].

Vitamin A
Among those at high risk of vitamin A deficiency are patients with malabsorption and fat-absorption disorders, such as celiac disease and short-bowel syndrome. The oral manifestations of vitamin A deficiency include xerostomia (dry mouth), reduced resistance to infections, and impaired growth of the teeth. The oral manifestations of toxicity include cheilitis, gingivitis, carotenemia (orange discoloration of the mucous

membranes due to excessive deposition of pigment), and impaired healing. Patients whose livers are compromised because of drug abuse, hepatitis, or excessive ingestion of carrots are at risk of vitamin A toxicity [49].

Vitamin D

Among those at high risk of calcium deficiency are the elderly, women who have had multiple pregnancies, and low-birthweight infants. Vitamin D deficiency may increase the loss of periodontal attachment [14, 49].

Vitamin E (Tocopherol)

Tocopherol is an antioxidant, deficiency of which may be associated with oral cancer. Those at high risk of vitamin E deficiency include premature infants and patients with malabsorption disorders or lipid transport abnormalities [14, 49].

Calcium

Those at high risk for calcium deficiency include premature infants who do not go through the critical intrauterine phase whereby 80% of the body's calcium, phosphorus, and magnesium are absorbed and who also may have malfunctioning kidneys that fail to metabolize vitamin D adequately. Low calcium intake is associated with an increased risk of periodontal disease. Conversely, increased calcium intake has been shown to be associated with decreased risk of periodontal disease and tooth loss, in part due to its role in preventing systemic bone loss [49].

Fluoride

Fluoride makes tooth enamel less soluble and more resistant to demineralization, so its deficiency is associated with an increased incidence of dental caries. However, toxicity causes mottling of the enamel, ranging from mild white flecks to extreme brown discoloration and enamel pitting [49].

Iron

Pregnant women and patients with unusual blood loss or malabsorption disorders are at elevated risk of iron deficiency. Oral manifestations of iron deficiency include atrophy of the lingual papillae, burning and redness of the tongue, angular stomatitis, dysphagia, and pallor of the oral tissues resulting from underlying anemia. Like folic acid and B12, iron deficiency may be associated with recurrent aphthous ulcers [28, 49]. Although the cause of Plummer–Vinson syndrome is still uncertain, this syndrome is associated with iron deficiency along with genetic factors, and presents with angular stomatitis, glossitis, and dysphagia [49].

Zinc

Those at high risk of zinc deficiency include pregnant women, the elderly, vegans, alcoholics, diabetics, and those with HIV/AIDS, inflammatory bowel disease, and sickle cell disease. Excessive consumption of calcium, iron, copper, fiber, phytates, and phosphate salts interferes with proper zinc absorption. Oral manifestations of zinc deficiency include changes to the epithelium of the tongue, an increase in cell numbers, and flattened filiform papillae, ulcers, and xerostomia. Impaired wound healing is one of the most damaging effects of zinc deficiency. Zinc enhances taste and appetite, so deficiency also results in decreased taste sensation, which can cyclically contribute to malnutrition. In AE, the oral mucous membranes may be secondarily infected with *Candida* or *Staphylococcus* [14, 49].

Skin Manifestations

The most frequent oral signs and symptoms of nutritional disorders are angular cheilitis, stomatitis, glossitis, burning mouth, gingival erythema, and dental caries. Individually or in combination, these manifestations could represent early symptoms of vitamin or element deficiency.

Complementary Examinations

Depending of the oral mucosa manifestations, the following serum tests should be considered: folic acid, vitamin B12, 25(OH)D, calcium, zinc, iron, and ferritin.

Therapeutic Approach

Vitamin and element deficiencies should be investigated and treated to resolve the oral signs and symptoms of the nutritional disorders. They will improve once the deficiency is eliminated [14, 49] (Table 38.1).

Nail Disorders

Nutritional Correlation

Several systemic diseases lead to nail changes that dermatologists can visually perceive. However, not all gross changes are secondary to malnutrition alone. Those nail changes attributable solely to malnutrition and other systemic diseases that could manifest secondary to a deficiency in a particular vitamin, mineral, or other trace element (e.g., iron deficiency anemia) are described below [14, 50] (Chart 38.1).

Chromonychia
Chromonychia of the lunula has been reported as a bluish discoloration in copper overload caused by Wilson's disease. Argyria, a chronic elevation of silver salts in the body, has been associated with a blackish-gray discoloration of the lunula and is thought to be photoinduced. Color changes in the nail bed are more diffuse than focal chromonychia of the lunula. Although nonspecific, pallor of the nail bed can be a sign of anemia and an indication that body iron stores may be low. Longitudinal melanonychia of the nail plate secondary to increased melanin production in the matrix has been reported in malnutrition, vitamin D and vitamin B12 deficiencies, and hemochromatosis [50].

Splinter Hemorrhages
Although classically associated with subacute bacterial endocarditis, these are most frequently seen as a result of trauma and have been associated with a number of systemic illnesses. Among the nutrition-related conditions are scurvy (vitamin C deficiency) and hemochromatosis [20, 50].

Terry Nails
Despite its classical association with chronic liver disease, Terry nails may also be seen in malnutrition states, especially in the elderly [50].

Muehrcke Lines
This condition was initially associated with hypoalbuminemia, but this nail change has also been associated with malnutrition and AE [15, 50].

Onycholysis
Onycholysis may be due to exogenous or endogenous causes, with the former representing most of the cases seen in clinics. Some endogenous causes of onycholysis related to nutritional imbalances include iron-deficiency anemia, pellagra, and Cronkhite-Canada syndrome, an extremely rare nonfamilial syndrome characterized by marked epithelial disturbances in the gastrointestinal tract and epidermis. The abnormal mucosal proliferation leads to fluid and electrolyte abnormalities, malabsorption, and malnutrition [20, 50].

Transverse Leukonychia
Although transverse leukonychia is typically associated with deficiency-related states such as AE, pellagra, and low calcium levels, it is also associated with overabundance, such as in the increased blood iron levels that occur in hemochromatosis (Fig. 38.4) [15, 50].

Clubbing
Clubbing can be inherited or acquired. An inherited type of clubbing that falls under the purview of nutritional imbalance includes citrullinemia, a rare autosomal recessive disorder of the hepatic urea cycle that leads to an accumulation of nitrogenous waste compounds and other toxic substances, including citrulline, in the blood. Acquired clubbing secondary to nutritional imbalance may be due to several different combinations of substances and pathologies, including phosphorus, arsenic, alcohol, mercury or beryllium poisoning, hypervitaminosis A, and cretinism caused by iodine deficiency [50].

Fig. 38.4 Transverse leukonychia (Courtesy of Dermatology Service of UFCSPA)

Koilonychia

Almost all cases of koilonychia are acquired, although it may be also inherited. It is classically a sign of iron-deficiency anemia and has not been observed in any other type of anemia. However, a few published cases have reported koilonychia in postgastrectomy patients and in patients diagnosed with Plummer–Vinson syndrome. These clinical syndromes have iron-deficiency anemia (e.g., iron malabsorption in postgastrectomy patients and iron-deficiency anemia as one criterion of the Plummer–Vinson syndrome clinical triad) and support the notion that koilonychia is observed only in sideropenic anemia and not in other anemias. Other nutritional states, such as riboflavin deficiency, pellagra, and more commonly, vitamin C deficiency, have been implicated in the development of koilonychia [20, 50].

Hapalonychia

This condition is also known as soft nails and may be associated with occupational diseases, eczematous dermatitis, and certain systemic diseases. Nutritional deficiencies involving vitamins A, B6 (pyridoxine), C, and D, in addition to low serum calcium, have all been implicated in causing hapalonychia [50].

Beau's Lines

Nutritional disorders associated with Beau's lines include protein deficiency and pellagra. Dysregulated blood mineral levels, such as hypocalcemia, chronic alcoholism (another source of malnutrition and malabsorption), and arsenic toxicity, may also play a role in the development of Beau's lines [20, 50].

Onychomadesis

The most common cause of onychomadesis is neurovascular change. Examples would be repeated episodes of decreases in blood calcium levels or a chronic state of hypocalcemia with arteriolar spasm. Such episodes may lead to an abrupt separation of the nail plate from the underlying nail matrix and nail bed, and results in the clinical manifestation of onychomadesis [50].

Onychorrhexis

Mineral imbalances leading to onychorrhexis include iron-deficiency anemia, arsenic poisoning, and zinc deficiency [50].

Trachyonychia

This condition is typically caused by poor or decreased dietary water and food intake, an especially common phenomenon in the elderly. Any of these may contribute to and precipitate the brittle nails and subsequent trachyonychia seen in the elderly [50, 51].

Skin Manifestations

Chromonychia may occur in the lunula, the nail bed, or the nail plate. The word is defined as any color (excluding white) that abnormally discolors a part of the nail unit. Because white is not necessarily considered a distinct color, whitened areas of the nail unit define the term leukonychia.

Transverse leukonychia is distinguished by transverse, opaque white bands that tend to occur

in the same relative position in multiple nails. These bands mimic the contour of the lunula and grow out with the nail plate.

Splinter hemorrhages are formed by extravasation of red blood cells from longitudinally oriented nail bed vessels into adjacent longitudinally oriented troughs.

Terry nails are described as any 0.5- to 3.0-mm wide, distal, brown-to-pink nail bed bands with proximal pallor.

Muehrcke lines are characterized by two transverse white bands of pallor. When pressure is applied to the distal plate, the narrow transverse bands disappear, confirming a nail bed change.

Onycholysis is defined as separation of the nail plate from the underlying nail bed.

Clubbing is the term is used when the normal 160° angle between the proximal nail fold and the nail plate exceeds 180°.

Koilonychia is defined as spoon-shaped nail plates. It is thought to result from a relatively low-set distal matrix compared with the proximal matrix that causes nail plate growth to occur in a downward direction as it grows toward the nail bed. When present, it is usually more severe on the index and third fingernails.

Beau's lines are defined as transverse grooves in or depression of the nail plate seen in acute systemic disorders. It is one of the most common signs encountered in clinical practice, but is the least specific. Acute illnesses are thought to cause a temporary arrest of the matrix. If the entire activity of the matrix is inhibited for 1–2 weeks, a Beau's line will reach its maximum depth, causing a total division of the nail plate (i.e., onychomadesis).

Onychomadesis is the term used to describe complete onycholysis, beginning at the proximal end of the nail plate.

Onychorrhexis, or senile nail, describes longitudinal ridges in the nail plate that are most often associated with the aging process.

The term trachyonychia describes rough nail plates with a characteristic gray opacity, brittle (fragilitas unguium) and split free ends, longitudinal ridging, and a rough sandpaper-like surface. Brittle nails and trachyonychia are relatively common in persons older than 60 years. Brittle nail syndrome is a disease characterized by soft, dry, weak, easily breakable nails that show onychorrhexis and onychoschizia [50].

Complementary Examinations

Depending of the nail disorder, the following serum tests should be performed: complete blood count, albumin, iron, ferritin, vitamin B12, 25(OH)D, calcium, zinc, phosphorus, and liver function tests.

Therapeutic Approach

Little information is available on how nutritional supplements affect different nail disorders. It is recognized that if there is a deficiency of any compound, it should be supplemented.

A multitude of regimens exist for treating brittle nails, including buffing and moisturizing, application of essential fatty acids, and the ingestion of vitamin C and pyridoxine, iron, vitamin D, calcium, amino acids, and gelatin. One nutritional supplement that has been investigated and has recently shown promise is biotin, or vitamin H. The use of biotin to strengthen horse hooves in veterinary medicine suggested it could be used to treat human nail disease. One study demonstrated a 25% increase in the thickness of the nail plate in patients diagnosed with brittle nails of unknown cause and treated with biotin (2.5 mg daily) for 6–15 months. Another study showed that biotin was not equally effective in all patients, but a definite trend toward benefit was noted in most of those who took between 1.0 and 3.0 mg daily, with 2 months being the average time before clinically noticeable results. This same study also showed that approximately 10 weeks after biotin was discontinued, nail ridging gradually returned and nail brittleness recurred. The daily requirement of biotin is unknown because it is produced in large quantities by intestinal bacteria. A daily dose of 2.5–3 mg of biotin for approximately 6 months is generally recommended [50, 51] (Table 38.1).

A healthy, well-balanced diet composed of an adequate daily intake of vitamins and minerals facilitates nail health in general. Nails are pure protein, so sufficient protein intake is necessary to ensure healthy nails. Many vegetarians find their nails are first to show the obvious effects of inadequate protein intake [51].

Topical silicon and tazarotene cream 0.1% have recently been advocated with mixed results for brittle nail syndrome [50, 51].

Necrolytic Migratory Erythema

Nutritional Correlation

Necrolytic migratory erythema (NME) is a rare cutaneous dermatitis that occurs most commonly in patients with a glucagonoma, an α-cell tumor of the pancreas, although it may occur in the absence of a pancreatic tumor (pseudoglucagonoma syndrome) in the context of other malignancies, liver disease, malabsorption disorders, and inflammatory bowel disease [36]. A number of hypotheses have been proposed concerning the pathogenesis of NME lesions. These include hyperglucagonemia, hypoaminoacidemia, zinc and/or EFAD, liver disease, induction of inflammatory mediators, and generalized malabsorption and malnutrition. It is likely that these theories are not mutually exclusive [20, 36, 38].

It has also been suggested that amino acid deficiency and zinc deficiency contribute to the pathogenesis of NME. Some patients with unresectable glucagonomas have decreased levels of amino acids and show improvement in cutaneous lesions after intravenous administration of amino acids. An improvement in the dermatosis has been observed after zinc supplementation and fatty acid supplementation, suggesting that various nutritional deficiencies may lead to the NME rash. Persistent stimulation of various metabolic pathways by high levels of glucagon may result in hypovitaminosis B and low levels of essential fatty acids and amino acids, thus contributing to the glucagonoma syndrome [20, 38].

Liver disease has been suggested to contribute to NME pathogenesis and lead to low albumin levels, which can produce deficiencies in zinc and essential fatty acids because albumin is their predominant carrier protein in the plasma [38].

Skin Manifestations

The clinical features of the rash include waves of irregular erythema in which a central bulla develops with subsequent erosion and crusting. Central healing occurs, which gives the lesions an annular appearance. The lesions are typically highly pruritic, and predominantly occur at intertriginous sites and areas subject to pressure and friction, such as the perineum, groin, buttocks, lower abdomen, and lower extremities. Stomatitis, glossitis, angular cheilitis, and nail changes may also be seen [38].

Complementary Examinations

Glucagonoma should be investigated, especially with serum glucagon and imaging examinations. Other important complementary examinations include blood glucose, albumin, zinc, liver function tests, erythrocyte sedimentation rate, and C-reactive protein.

Therapeutic Approach

As improvement in the NME rash has been seen after administration of amino acids, zinc, and fatty acid supplementation, deficiency in any of these elements should be corrected [38].

Pellagra

Nutritional Correlation

Pellagra is a systemic nutritional wasting disease caused by a deficiency of vitamin B3 (niacin), which is an essential component of several coenzymes. Besides ingestion, niacin can be endogenously synthesized from its natural precursor, the amino acid tryptophan, a process that requires

two other B vitamins, B2 and B6. Pellagra occurs when the intake of niacin and tryptophan are low (primary) or when conversion of the essential amino acid to the coenzyme (secondary) is impaired [14] (Chart 38.1).

At present, pellagra is limited to populations with a compromised dietary intake of niacin and tryptophan or an excessive intake of leucine (a natural antagonist), especially in times of stress or in unique circumstances. These situations include chronic alcohol intake, individuals with significant malabsorption, administration of specific medications, or with a few rare disease entities that affect niacin availability [52].

Skin Manifestations

Classically, patients with pellagra have a syndrome that includes diarrhea, dermatitis, and dementia. The distribution of the cutaneous eruption is typically symmetric and bilateral in parts of the body exposed to sun. The dorsal areas of the hands are the most affected sites, which may present a glove-like distribution; the classic Casal's necklace and neck lesions are also seen. Other skin manifestations linked to niacin deficiency are glossitis and angular and lip cheilitis [52].

Complementary Examinations

Low serum niacin and tryptophan are thought to reflect niacin deficiency and confirm the diagnosis of pellagra.

Therapeutic Approach

Pellagra is often an evolving process, which, if untreated, can lead to progressive deterioration and death over a period of years. Therapeutic response to niacin in a patient with the typical symptoms and signs of pellagra establishes the diagnosis. The recommended intake of 6.6 niacin equivalents per 1,000 kcal daily is accepted for children aged 6 months or older. For infants up to 6 months, it is accepted that breastfeeding by well-nourished mothers supplies adequate

niacin equivalents to fulfill the needs (i.e., 8 niacin equivalents/1,000 kcal) of this age group. A diet high in protein and adequate in calories should be provided in order to prevent and/or treat pellagra. The addition of meats, milk, peanuts, green leafy vegetables, whole or enriched grains, and brewers' dried yeast can enhance niacin intake. The treatment of adult pellagra is nicotinic acid 50–100 mg orally every 6–8 h, not to exceed 500 mg/day [14, 52] (Table 38.1).

Skin Manifestations of Peripheral Vascular Disease

Nutritional Correlation

Peripheral vascular disease (PVD) is a nearly pandemic condition and manifests as insufficient tissue perfusion initiated by existing atherosclerosis acutely compounded by either emboli or thrombi. The atheroma consists of a core of cholesterol joined to proteins with a fibrous intravascular covering. The most important causes of atherosclerosis are high fat levels in the blood, diabetes, and high blood pressure. The disease is typically segmental, with significant variation from patient to patient [53, 54].

Obesity is an important factor in varicose veins. Stasis pigmentation is the result of the escape of red blood cells into surrounding tissues, which results in an inflammatory reaction to the deposited hemoglobin [53, 54].

Skin Manifestations

In PVD the skin may have an atrophic, shiny appearance and may demonstrate trophic changes, including alopecia; dry, scaly, or erythematous skin; chronic pigmentation changes; and brittle nails. Advanced PVD may manifest as livedo reticularis (mottling), pulselessness, numbness, or cyanosis. Paralysis may follow, and the extremities may become cold; gangrene may occasionally be seen. Poorly healing injuries or ulcers in the extremities help provide evidence of pre-existing PVD [53, 54].

Clinically, in the presence of varicose veins pitting edema usually occurs at the extremities, but varicose veins are not always apparent. There is dark pigmentation and often extensive scaling of the skin. The legs may also be red, warm, and tender because of an inflammatory reaction to the pigment in the dermis. Signs, such as small erosions to very large ulcers, may represent the residue of an underlying eczematous dermatitis, but deep ulcers are uncommon. In most cases, the ulcers occur on the medial ankle or lower calf and usually have a red base of granulated tissue. The subcutaneous tissue may be indurated (Fig. 38.5) [53, 54].

Complementary Examinations

Plain films are of little use in the setting of PVD. Doppler ultrasonographic studies are useful as primary noninvasive studies to determine flow status. Upper extremities are evaluated over the axillary, brachial, ulnar, and radial arteries. Lower extremities are evaluated over the femoral, popliteal, dorsalis pedis, and posterior tibial arteries. One should note the presence of Doppler signal and the quality of the signal (i.e., monophasic, biphasic, triphasic). The presence of distal flow does not exclude emboli or thrombi because collateral circulation may provide these findings.

Therapeutic Approach

At present, therapeutic recommendations include single-agent antiplatelet agents for the prevention of cardiovascular events in patients with asymptomatic and symptomatic disease. These medications should be used in conjunction with efforts to reduce risk factors, including adequate diet with low fatty foods, smoking cessation, and exercise therapy. In the case of obesity, weight reduction is necessary to lower peripheral venous pressure [53, 54].

Phrynoderma and Vitamin A Deficiency

Nutritional Correlation

Vitamin A is a liposoluble vitamin that is vital for retinal photoreceptors and the correct functioning of the immune system, as well as skin keratinization and the process of embryogenesis. Vitamin A intake may be inadequate in patients with restrictive diets and EDs. Although vitamin A deficiency is more common in underdeveloped countries, in developed countries its manifestations can be induced by liver cirrhosis, malnutrition, or alcoholism. Liver disease patients evaluated for liver transplantation often have vitamin A deficiency. Both dietary quality and diversity may deteriorate in economic crises. Nevertheless, vitamin A deficiency remains preventable during economic instability by promoting breastfeeding, providing supplementary vitamin A, fortifying foods targeted at the poor, and encouraging homestead food production that can bolster income and diversify the diet. Early dietary intervention, preferably within the first 1,000 days of life, is important to break the cycle of malnutrition and its undesirable consequences [6, 55].

Vitamin A is also important in cellular differentiation (e.g., growth, reproduction, immune response) and in maintaining epithelial integrity. No nutritional deficiency is more synergistic with infection than vitamin A. The two main mechanisms involved in the prevention of disease are the effect of vitamin A on the immune system and on epithelial integrity. Epidermal vitamin A deficiency may result from a deficit of nutritional vitamin A, exposure to sunlight or any ultraviolet (UV) source, oxidative stress, or chronologic aging. Accordingly, increasing epidermal vitamin A may be beneficial [6, 55].

Phrynoderma has been considered pathogno-monic of vitamin A deficiency, but probably represents a nonspecific finding common to cases of nutritional insufficiency, as it has also been associated to fatty acid, vitamin E, and vitamin B2 deficiencies [6, 14] (Chart 38.1).

Skin Manifestations

Phrynoderma is characterized by follicular and keratotic papules that usually affect the anterolateral surface of the thighs and arms. Lesions may overtake the extensor surface of the upper and lower limbs, shoulders, abdomen, dorsal area, buttocks, and neck. Other cutaneous manifestations associated with vitamin A deficiency are xeroderma and thinning, brittle, or corkscrew hair. The correlation between low plasma concentrations of vitamins A and E and the development of acne has recently been speculated [6, 55].

Complementary Examinations

The diagnosis should be suspected in children who are malnourished or in patients with predisposing factors for its development. The following are employed to evaluate serum vitamin A levels:

- The biochemical definition of vitamin A deficiency is a plasma level of 35 μmol/dL or less. Several techniques are available, but high-pressure liquid chromatography is the most reliable. An important factor is that, with protein deficiency, serum vitamin A levels may be decreased despite good vitamin A intake and adequate vitamin A stores.
- Total and holo retinol-binding protein test in the blood tend to correlate with measures of serum vitamin A. These levels can also be decreased in the presence of protein deficiency.

Therapeutic Approach

Oral administration of 200,000 IU of vitamin A at presentation, the following day, and a third dose a week later is recommended. Children younger than 1 year should receive one-half the standard dose, and infants younger than 6 months should receive one-quarter the standard dose. Children with marasmus or kwashiorkor need further nutritional supplementation and monitoring with additional doses of vitamin A at monthly intervals until clinical improvement. Pregnant women should not receive large doses of vitamin A because it may be teratogenic, but a daily dose of 10,000 IU over 2 weeks is safe. In all cases, a diet rich in vitamin A should be advised [14] (Table 38.1).

Porphyria

Nutritional Correlation

Dietary factors have been implicated in triggering porphyria and also as potential photoprotective agents [20, 57].

Porphyria Cutanea Tarda
Porphyria cutanea tarda (PCT) is the most common form of porphyria. A variety of factors have been associated with this disease, namely alcohol, estrogens, polychlorinated hydrocarbons, abnormal iron metabolism, and viral infections, including hepatitis C and HIV. Several dietary factors have been suggested as having a protective role in PCT [20, 38, 56, 57].

Alcohol
The effects of alcohol on porphyrin metabolism and heme biosynthesis enzymes have been investigated in many studies. Alcohol is a frequent factor in triggering and aggravating porphyrin metabolism disorders, both in acute and chronic porphyria. Alcohol is believed to have an inhibitory effect on uroporphyrinogen decarboxylase, either directly (affecting heme biosynthesis) or through an iron-dependent mechanism [38, 57].

Iron
Iron concentrations (total body and hepatic non-heme) are increased in almost 65% of patients, whereas iron depletion by repeated phlebotomy, chelators, or decreased intake is protective. Phlebotomy is effective in patients with normal

body iron stores, suggesting that possible changes in iron homeostasis may contribute to the pathogenesis of PCT [38].

Antioxidants

Deficiency in ascorbic acid (vitamin C) and other antioxidant factors has been proposed to play a role in some patients with PCT. One study showed a significant decrease in α- and β-carotene as well as cryptoxanthin and lycopene in PCT patients. There is conflicting evidence regarding vitamin E [20, 38].

Variegate Porphyria

In acute porphyria, acute attacks can be triggered by stress, menstrual cycle, drugs, chemicals, alcohol, smoking, and fasting, among others. Diet and dietary factors also influence the manifestations of acute porphyria. Fasting or carbohydrate restriction through dieting has been shown to trigger attacks of acute porphyria. This occurs due to increased demand for hepatic heme and an induction in the first enzyme of the heme biosynthetic pathway, aminolevulinic acid synthase, resulting in increased production of heme pathway intermediates. Carbohydrate loading has an inhibitory effect on aminolevulinic acid synthase and has been used as a standard treatment for acute attacks [20, 38, 57].

Hereditary Coproporphyria

As with variegate porphyria, alcohol and fasting can trigger acute attacks, and the avoidance of alcohol and the adoption of a balanced diet are recommended. Carbohydrate loading or glucose loading is beneficial during acute attacks [20, 38].

Congenital Erythropoietic Porphyria

Oral β-carotene has been used as a photoprotective agent with benefit in some patients. Ascorbic acid and α-tocopherol have also been used to quench reactive oxygen species, with some beneficial effects on hemoglobin and erythrocyte levels with long-term therapy [38].

Erythropoietic Protoporphyria

This is the second most common cutaneous porphyria after PCT. A number of dietary factors, most notably β-carotene, have been used as treatment options for the photosensitivity in erythropoietic protoporphyria [20, 38].

A normal diet contains about 40 carotenoids, of which 12 are absorbed in the intestine (α-carotene, β-carotene, lutein, zeaxanthin, β-cryptoxanthin, and lycopene being the most common). β-Carotene has been used for more than 30 years as a photoprotective agent in various photosensitivity disorders and is recommended for the photoprotection of patients with erythropoietic protoporphyria. β-Carotene is believed to quench the singlet oxygen and reactive oxygen species produced subsequent to activation of protoporphyrin by visible light. Dietary sources include yellow and green vegetables, carrots, tomatoes, spinach, sweet potatoes, fruit, and algae [38].

A recent in vitro study analyzed the protective capability of the antioxidants lycopene, β-carotene, ascorbic acid, and α-tocopherol against porphyrin phototoxicity in cell culture experiments. Lycopene provided benefit against protoporphyrin phototoxicity and, in addition, there was an increased protective effect of β-carotene in the presence of ascorbic acid and α-tocopherol, suggesting antioxidant synergy. In vivo studies are required to determine the clinical significance of these findings [20, 38].

Dietary fish oils rich in omega-3 polyunsaturated fatty acids are promising systemic photoprotective agents. There is one case report of an erythropoietic protoporphyria patient who improved with a dietary supplement of fish oils [38].

Skin Manifestations

In cutaneous porphyria there is excessive formation of porphyrins, which photosensitize human skin. With the bullous form there is fragility of exposed skin, blistering, and erosions which lead to scarring, hyperpigmentation and hypopigmentation, and milia (Fig. 38.6). Hypertrichosis and morpheaform areas may also develop on the face and chest. With immediate photosensitivity, severe burning-type pain areas, accompanied by visible edema, develop within minutes of sun exposure. Five main types of cutaneous porphyria
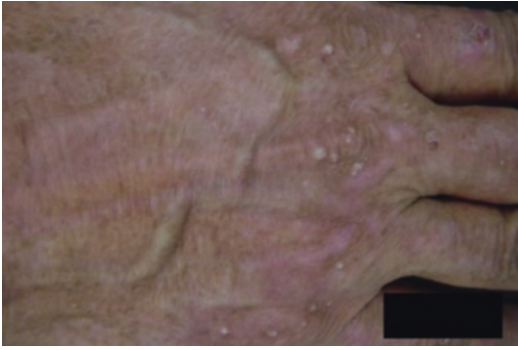
Fig. 38.6 PCT: fragility of exposed skin, erosion, erythema, hyperpigmentation and hypopigmentation, and milia on the hand (Courtesy of Dr. Renan R. Bonamigo)

have been described: PCT, variegate porphyria (mixed porphyria), hereditary coproporphyria, congenital erythropoietic porphyria, and erythropoietic protoporphyria. The latter type presents with acute photosensitivity, whereas the other types show the typical bullous skin changes [57].

Complementary Examinations

Besides the appropriate diagnosis of each type of porphyria, it is important to evaluate the following serum tests: iron, ferritin, liver function tests, and exclusion of hepatitis and HIV infection.

Therapeutic Approach

Avoidance of alcohol is important, both therapeutically and prophylactically, in porphyria patients [20, 38, 57].

There is conflicting evidence regarding the benefits of vitamin E treatment in PCT. Some authors have reported successful treatment with high doses of vitamin E, while others reported no such effect. Similarly, β-carotene has not proved to be useful in treating PCT. More studies are needed to evaluate whether antioxidant supplements can be used as a therapeutic approach to PCT [20, 38].

A recent report evaluated the effects of a high-fiber vegetable and fruit diet in 13 PCT patients. The diet showed a beneficial effect on the severity of skin lesions after 3 weeks. A significant decrease in urinary coproporphyrins was also noted, although there was no significant change in iron levels. More studies are needed to determine whether this diet could be useful in PCT patients [38].

A high-carbohydrate diet is recommended in patients with acute porphyria [20, 38].

The role of oxidative stress in variegate porphyria has not been fully elucidated, and it is unclear whether supplementation with antioxidant nutrients is beneficial for the patients [20, 38].

In hereditary coproporphyria a balanced diet is recommended, and carbohydrate loading or glucose loading is beneficial during acute attacks [38].

The US Food and Drug Administration approved β-carotene for the treatment of erythropoietic protoporphyria in 1975, and it has been widely used since then in these patients and in congenital erythropoietic porphyria. However, the evidence to prove its efficacy has been somewhat contradictory. While a few small studies have supported its use, the only controlled trial failed to show benefits. Although more studies are needed to assess the efficacy of β-carotene, it remains a mainstay of erythropoietic protoporphyria therapy due to its ease of administration and possible beneficial effects. High doses are recommended (120–180 mg/day in adults) to achieve the desirable plasma level of 600–800 μg/dL, and discontinuation of therapy is suggested after 3 months if the therapy is ineffective. Further studies with more patients are needed to assess the effects of fish oils, vitamin C, and vitamin E [20, 38].

Some small studies have attempted to evaluate the role of cysteine, *N*-acetylcysteine, and pyridoxine as photoprotective agents in erythropoietic protoporphyria patients, but the results are controversial [38].

Pressure Ulcers

Nutritional Correlation

The National Pressure Ulcer Advisory Panel defines a pressure ulcer (PU) as an area of unrelieved pressure over a defined area, usually over a

bony prominence, resulting in ischemia, cell death, and tissue necrosis. Obese patients may be at particular risk of developing PUs. Malnourished patients given a specific nutritional supplement showed improvement in the size of their PUs in a recent multicenter RCT, although previous trials had not shown the same effects with similar ingredients. Both experimental and control groups were given a high-calorie, high-protein supplement, but the experimental group's supplement also contained high levels of zinc, arginine, and a group of antioxidants: selenium, manganese, and vitamins C and E. The rate of complete healing of PUs did not differ among the groups, but patients who received the extra micronutrients showed a greater decrease in the area of their wounds. Despite this reduction in the size of their PU with the use of supplements, the researchers found no difference in the secondary outcomes of the study, including complete healing or the incidence of infections [53, 54].

Skin Manifestations

The clinical presentation of pressure ulceration can be deceptive to the inexperienced observer. Soft tissue, muscle, and skin resist pressure to differing degrees. In general, muscle is the least resistant and will become necrotic before skin breaks down. Also, pressure is not equally distributed from the bony surface to the overlying skin; it is greatest at the bony prominence, decreasing gradually toward the periphery. A small area of skin breakdown may represent only the tip of the iceberg, with a large cavity and extensive undermining of the skin edges beneath [53, 54].

Complementary Examinations

A complete blood count with differential may show an elevated white blood cell (WBC) count indicative of inflammation or invasive infection. The erythrocyte sedimentation rate (ESR) should be determined. An ESR higher than 120 mm/h and a WBC count greater than 15,000/μL suggest osteomyelitis.

Nutritional parameters should be evaluated to assess adequate nutritional stores needed for adequate wound healing. Useful tests include the following: albumin level, prealbumin level, transferrin level, and serum protein level.

Therapeutic Approach

Nutritional and functional status should be assessed in all patients (hospitalized, obese, or malnourished patients), whereby physicians and health professionals are able to identify individuals at risk of developing PU.

Nonsurgical treatment measures include the following: pressure reduction; wound management (debridement, cleansing agents, dressings, and antimicrobials); and newer approaches, still under study (growth factors, negative-pressure wound therapy, and electrotherapy) [53, 54].

Psoriasis

Nutritional Correlation

The role of nutrition in the treatment of psoriasis has been studied for many years. Most recently, the observation of comorbid conditions associated with psoriasis has stimulated renewed interest in nutrition as a better way to approach the disease [6, 20, 58, 59].

The efficacy of vitamin A and vitamin D derivatives has been well established. As adjuvant therapy, changes in dietary behavior may help augment the effect of well-established treatments. Limitation of alcohol use, adoption of a low-calorie or gluten-free diet, or treatment of comorbid conditions, when applicable to a particular patient, may hasten the clearing of psoriatic lesions in patients undergoing phototherapy or receiving topical or systemic medications. Vitamin B12 and select antioxidants may also provide some benefit. Although many dermatologists often overlook the role of nutrition in the treatment of psoriasis, consideration of nutritional alternatives in select patients may help to enhance care [20, 28, 58].

Weight Loss

Metabolic syndrome is more common among psoriasis patients. An obesity induced proinflammatory state may exacerbate psoriasis symptoms, and psoriasis itself may contribute to weight gain, partially because of social isolation, unhealthy dietary habits, and reduced physical activity. In various clinical studies, weight loss appears to significantly improve psoriasis symptoms and the efficacy of some psoriasis medications, such as biological agents [6, 28, 59].

Alcohol

The relationship between psoriasis and alcohol consumption is complex and multifactorial. Evidence suggests that alcohol triggers and worsens psoriasis and that alcohol abuse is more common among patients with psoriasis [28, 58, 59].

Polyunsaturated Omega-3 Fatty Acid (PUFA)

Arachidonic acid, which is elevated in psoriatic lesions, is converted to leukotriene B4, a potent proinflammatory mediator. PUFAs, such as eicosapentaenoic acid and docosahexaenoic acid, are metabolized to leukotriene B5, a considerably weaker inflammatory molecule. Increased levels of PUFAs are postulated to decrease inflammation and improve psoriasis symptoms. Studies investigating the effect of fish or fish oil supplementation on psoriasis have produced inconsistent results. Several small studies reported improvement of cutaneous lesions and psoriatic arthritis, and a decrease in the side effects of psoriasis medications, after oral supplementation with fatty fish or fish oil [28, 59].

Gluten

Celiac disease and psoriasis are reported to occur simultaneously. For psoriasis patients with celiac-specific antibodies, a gluten-free diet improves psoriasis lesions [20, 28, 59].

Folic Acid

An increased incidence of folic acid deficiency has been reported in psoriasis patients. This observed deficiency may be related to elevated homocysteine levels, decreased intestinal absorption caused by inflammation, and/or increased use by skin epidermal cells. Folate deficiency is also implicated in psoriasis severity. Folate supplementation has been postulated to have an antithrombotic and cardioprotective role in some psoriasis patients. A recent review article, however, found insufficient evidence to support such a hypothesis. Folate supplementation may also be useful for psoriasis patients who have been treated with methotrexate. It was found to diminish adverse side effects of methotrexate therapy, such as hepatotoxicity and gastrointestinal intolerance.

Notably, a reduction in the efficacy of methotrexate with concurrent folate supplementation has also been reported [59].

Vitamin D

The utility of topical vitamin D in the treatment of psoriasis is well established, but the role of oral vitamin D supplementation remains unclear. A correlation between low serum vitamin D levels and increased severity of psoriasis has been suggested. Observational studies have shown the safety and efficacy of oral vitamin D supplementation in the treatment of psoriatic lesions and psoriatic arthritis. Notably, a recent randomized, placebo-controlled trial found no significant difference in the improvement of skin lesions in patients treated with oral vitamin D compared with controls [58, 59].

Selenium and Other Antioxidants

Increased oxidative stress and circulating free radicals may contribute to the inflammatory state of psoriasis. Antioxidants, particularly selenium, vitamin E, and β-carotene, can offset this oxidative imbalance. However, the evidence supporting the amelioration of psoriasis symptoms after antioxidant use is weak. Selenium supplementation has been studied most extensively. Selenium is essential for the normal functioning of glutathione peroxidase and may be found in low levels in patients with psoriasis, particularly those with extended disease duration. Some patients failed to show improvement

of clinical symptoms after supplementation with selenium-enriched yeast and combined selenium and vitamin E. Combination antioxidant therapy with selenium, coenzyme Q10, and vitamin E, on the other hand, was associated with rapid clinical improvement and reduction of cell markers of oxidative stress [28, 58, 59].

Inositol and Zinc

A randomized, placebo-controlled, double-blind trial demonstrated a significant improvement in the clinical score of lithium-treated patients taking inositol (6 g/day) versus a lactose placebo for 10 weeks. Zinc supplementation, however, did not produce significant improvement in the psoriasis clinical score in well-designed clinical trials [58, 59].

Taurine

Although early observations suggested that the amino acid taurine was involved in the pathogenesis of psoriasis, a series of studies failed to confirm that excessive or restricted taurine could exacerbate or ameliorate, respectively, the clinical course of psoriasis [58].

Skin Manifestations

Psoriasis is a chronic disease of abnormal keratinocyte proliferation and differentiation, as well as localized and systemic inflammation. The main skin features are sharply demarcated, scaly erythematous plaques, and, occasionally, sterile pustules. The pathogenesis is multifactorial, allowing for multiple therapeutic options.

Complementary Examinations

Psoriasis is associated with overweight/obesity and related cardiometabolic complications. In this context, such diseases should be excluded with blood glucose, lipid profile, echocardiography, and carotid Doppler echography. Other complementary examinations that should be performed include folic acid and selenium.

Therapeutic Approach

Dermatologists should encourage overweight and obese psoriasis patients to attempt weight loss and undertake increased physical activity to improve psoriasis symptoms, comorbid metabolic syndrome, and medication efficacy [6, 28, 58, 59].

Given the prevalence of alcohol use among patients with psoriasis, screening for abuse is advised [6, 20].

Dietary supplementation with polyunsaturated fatty acids, folic acid, vitamin D, and antioxidants can be considered as adjuncts in the management of some psoriasis patients. RCTs have produced conflicting results, necessitating additional studies before definitive recommendations can be made [28, 59].

Screening should be considered for celiac disease, and implementation of a gluten-free diet may improve both conditions if they are present simultaneously [20, 59].

Despite a few promising studies, consistent evidence supporting fatty fish diet or fish oil, vitamin D, folate, and antioxidant supplementation is currently lacking, and additional studies are required before concrete recommendations can be made [59].

Rosacea

Nutritional Correlation

The opinion that food aggravates rosacea has been accepted. Patients are counseled to avoid rosacea triggers and, thus, refrain from such items as spicy foods, alcoholic beverages, and hot, caffeinated drinks. The list of triggers may be more extensive and has been reported to include fruits, marinated meats, and cheeses. With regard to alcohol ingestion in rosacea patients, a survey found red wine as the most likely culprit, followed by distilled spirits, with beer as the least likely to cause symptoms in patients. With regard to spices, cayenne pepper aggravated rosacea 36% of the time, red pepper

34%, black pepper 18%, white pepper 9%, and paprika 9% of the time. In the fruit/vegetable category, citrus items and tomatoes were most often identified as triggers [6, 60].

In addition to particular food types triggering rosacea, the temperature of food and beverages can also be an aggravating factor. For years, patients have been told to avoid hot, caffeinated beverages such as coffee and tea, and although caffeine may aggravate rosacea, there is now quantitative evidence that heat is a true culprit. Therefore, for many patients an iced coffee or tea may be less of a trigger than originally thought [60].

Another novel dietary influence in rosacea patients may be the omega-3 and omega-6 fatty acids. Recently, in the ophthalmology literature, evidence has shown that supplements or foods that contain such fatty acids may help with dry eyes. Some dermatologists have been using flaxseed oil, which contains high levels of omega-3 fatty acid, to help combat ocular rosacea [20, 60].

Skin Manifestations

Rosacea is a common condition characterized by facial flushing and a spectrum of clinical signs, including erythema, telangiectasia, coarse skin, and an inflammatory papulopustular eruption resembling acne [6, 60].

Complementary Examinations

The diagnosis is made clinically.

Therapeutic Approach

Clearly the impact of diet on rosacea is more widely accepted and documented than is the case with acne. Thus, patients with this condition should be encouraged to keep a food diary to help them elucidate possible triggers. With little effort, physicians can encourage such diaries and the avoidance of triggers [14, 60].

Scurvy and Vitamin C Deficiency

Nutritional Correlation

Vitamin C, also known as ascorbic acid, is a water-soluble vitamin required for the synthesis of collagen, L-carnitine, and neurotransmitters. It is also involved in protein metabolism. Vitamin C is a strong antioxidant and has been shown to regenerate other antioxidants such as vitamin E, and also plays an important role in immune function and improves the absorption of nonheme iron. Vitamin C cannot be produced by humans but is readily available in many types of food. Citrus fruits are the best known sources of vitamin C, but red and green peppers, tomatoes, potatoes, and other vegetables are also excellent sources [14, 61, 62].

Vitamin C deficiency leads to scurvy. Humans, unlike other animals, are unable to produce vitamin C and therefore depend on dietary sources. Scurvy has been described since ancient times and is best known for its high incidence in sailors. In the 1700s, addition of citrus fruit to the diet of sailors largely cured scurvy in that group, but there were still incidents of "land scurvy" in populations with abnormal diets. Today, scurvy is extremely rare because of improved food supplies, vitamin-fortified foods, and vitamin supplements, but can occur in populations with poor diets. The main function of vitamin C is in the triple-helix formation of collagen; vitamin C deficiency impairs collagen synthesis and results in the typical signs of scurvy [14, 61] (Chart 38.1).

Skin Manifestations

The first signs are fatigue, malaise, and lethargy. The first cutaneous disorder is keratosis pilaris on the lateral and posterior areas of the arms, buttocks, and thighs. These lesions may become hemorrhagic, particularly in areas of pressure. The main changes in the oral cavity

are the presence of edematous, erythematous, and friable gingivae with a tendency to bleeding. Symptoms can mimic SS with xerosis and keratoconjunctivitis. Other findings include conjunctival and gastrointestinal bleeding, ungual linear hemorrhage reflecting the weakness of blood vessel walls, osteochondral changes, and thinning corkscrew hair [14, 61, 62].

Complementary Examinations

Laboratory tests are usually not helpful to ascertain a diagnosis of scurvy. Presentation of an infant with the typical clinical and radiologic picture of scurvy, along with a supportive history of dietary deficiency of vitamin C, is often sufficient to diagnose infantile scurvy. Plasma ascorbic acid level may help in establishing the diagnosis, but this level tends to reflect the recent dietary intake rather than the actual tissue levels of vitamin C. Signs of scurvy can occur with low-normal serum levels of vitamin C. The best confirmation of the diagnosis of scurvy is its resolution following vitamin C administration. Noninflammatory perivascular extravasation of red cells and deposition of hemosiderin near hair follicles with intrafollicular keratotic plugs and coiled hair may be seen in a skin biopsy specimen.

Therapeutic Approach

Upon administration of adequate oral vitamin C, the symptoms of scurvy resolve within 1–12 days. Dosage forms are: males: 90 mg/day; females: 75 mg/day; pregnant women: 85 mg/day, not to exceed 2,000 mg/day (80 mg if <18 years; not to exceed 1,800 mg/day); nursing women: 120 mg/day, not to exceed 2,000 mg/day (115 mg if <18 years old; not to exceed 1,800 mg/day) [14] (Table 38.1).

Anemia, secondary to blood loss, is a common finding in scurvy and is usually associated with folate and iron deficiencies.

Skin Cancer

Nutritional Correlation

The role of diet and nutrition in carcinogenesis and, as a potentially modifiable factor, in cancer prevention is still under debate. The identification of a nutrient supplement with cancer-preventive properties would be a major breakthrough for public health. However, cancer is not a uniform disease and the existence of such a nutrient, or combination of nutrients, has been debated [6, 7].

Nonmelanoma Skin Cancer (NMSC)

Vitamin A
Multiple interventional studies have evaluated the effect of retinol, isotretinoin, or β-carotene on NMSC incidence. Studies found no significant difference in NMSC incidence between intervention and control groups after β-carotene supplementation. The study results for retinol and synthetic retinoids are more varied. Another study revealed no significant difference in time to first NMSC or in total number of tumors in retinol-treated versus control high-risk patients. Conversely, in patients with moderate risk, oral retinol supplementation significantly decreased the hazard ratio for first squamous cell carcinoma (SCC), but did not affect basal cell carcinoma (BCC) risk. Similarly, 10 mg of isotretinoin daily did not affect BCC development. Smaller studies of isotretinoin in patients with xeroderma pigmentosum and acitretin in renal transplant patients identified statistically significant reductions in NMSC incidence in treatment groups. These studies suggest that the impact of retinol and synthetic retinoids on NMSC may be affected by individual patient risk factors and comorbidities [63–65].

Vitamin D
In vitro studies in NMSC lines reveal differential expression and downstream effects of key components of the vitamin D system. Loss of the vitamin D receptor enhances susceptibility to

UV-induced tumorigenesis in mice. Vitamin D inhibits the hedgehog signaling pathway and upregulates nucleotide excision repair enzymes, potentially protecting against NMSC. Despite evidence from animal and in vitro studies, human studies are conflicting. One case–control study found an inverse relationship between vitamin D level and the risk of NMSC. Conversely, other studies identified a significant positive association between plasma vitamin D levels and NMSC risk. Sun exposure may confound these results, because UV radiation simultaneously increases serum vitamin D levels and promotes DNA mutations that are key in the development of skin cancer [7, 64, 66].

Vitamin E

Decreased plasma levels of α-tocopherol were found in patients with actinic keratosis and BCC compared with controls. Inverse associations between vitamin E dietary intake and supplementation and subsequent BCC development were observed. Conversely, two cohort studies found a positive association between dietary and supplemental vitamin E and BCC development, while others were unable to identify an association between vitamin E supplementation or serum levels and subsequent NMSC. In addition, a double-blind, placebo-controlled study found no clinical or histologic difference in response to UVB after 6 months of daily oral α-tocopherol (400 IU) supplementation [7, 64].

Vitamin C

In vitro studies of human keratinocyte cell lines show that ascorbic acid, which is a stable form of vitamin C, decreases UVB-induced cytotoxicity as a free radical scavenger and a potentiator of α-tocopherol-induced antioxidative activity. Vitamin C administration significantly inhibits UV-induced DNA, RNA, and protein synthesis in BCC and SCC cell lines in mice and rats. The photoprotective properties of topical vitamin C have been shown in porcine skin. In humans, studies of vitamin C and NMSC are inconsistent. Inverse relationships between the consumption of foods containing vitamin C, vitamin C supplements, and plasma levels of ascorbic acid with

NMSC were identified in three case–control studies. Conflicting results were obtained in two cohort studies that identified a positive association between BCC and the intake of vitamin C rich food or supplements. In addition, three case–control studies and five cohort studies failed to identify a significant association between vitamin C and NMSC [7, 67].

Selenium

Selenium protects against UVB-induced cytotoxicity in human keratinocytes and carcinogenesis in mice. Studies have found a potentially protective role of selenium for NMSC. In a case–control study, the mean plasma selenium level was significantly lower among NMSC cases than controls. Similarly, a cohort study found an inverse relationship between serum selenium concentration and subsequent NMSC. Finally, in a study of eight women treated with topical L-selenomethionine for 2 weeks, a significant increase in the minimal erythema dose after UV irradiation was observed, suggesting a possible photoprotective effect of topical selenium. The only RCT that has investigated the impact of oral selenium supplementation on NMSC found no significant association with the risk of BCC, but, interestingly, elevated risks of SCC and total NMSC. Other studies found no significant association between dietary or plasma selenium and NMSC [7, 68].

For women, there is little evidence for lower or higher nutritional intake of selenium exhibiting a major impact on cancer risk. The only RCT results that have a low risk of bias support concerns an increased risk of NMSC by selenium yeast supplements in women who had already suffered from this disease. For men, there is evidence for an inverse association between higher selenium biomarker levels and cancer risk. However, we cannot exclude the possibility that this effect may well be the result of other factors related to higher selenium biomarker levels than selenium exposure itself. Results from two RCTs have failed to provide evidence that NMSC or prostate cancer can be prevented by selenium supplementation in men. In addition, concerns have been

raised about possible toxicities from the long-term intake of supplemental selenium. At present, regular intake of selenium supplements for cancer prevention cannot be recommended to either the selenium-replete or -deficient populations [7, 68].

Low-Fat Diet

A study of patients who were following a low-fat diet found no significant difference in NMSC; therefore, a fat-restricted diet should not be recommended for NMSC prevention [7].

Melanoma

Polyunsaturated Fatty Acids

PUFAs are anti-inflammatory molecules that protect against UV damage. PUFA supplementation decreases skin sensitivity to UV irradiation and cutaneous expression of p53 in animal and human studies. Additionally, in animal and in vitro studies PUFAs were shown to increase apoptosis, promote cell-cycle arrest, and decrease tumor growth. PUFAs can inhibit metastatic melanoma, and when used as an adjunct to surgery promote recurrence-free survival. Some animal studies of PUFA supplementation found increased tumor growth and immunosuppression. These conflicting results of in vitro and animal studies do not elucidate a protective role of PUFAs against melanomagenesis. Clinical data are also conflicting. Studies, including two case–control trials and one prospective cohort study, reported an increased risk of melanoma in patients with higher dietary PUFA intake. In contrast, the incidence of melanoma is low in populations with PUFA-rich diets, including Inuits and cohorts in both Italy and Australia [7, 59].

Alcohol

The role of alcohol consumption in melanomagenesis is complex and involves the interplay of biological, behavioral, and epidemiologic factors. From a cellular standpoint, ethanol induces DNA damage and promotes the production of reactive oxygen species. Hormonal effects of ethanol include promoting prostaglandin synthesis and the secretion of melanocyte-stimulating

hormone. Finally, alcohol consumption alters immune function and increases the metastatic potential and growth of melanoma cells. Several large, population-level studies have found a positive association between alcohol consumption and melanoma risk. In fact, a recent systematic review reported a 20% increase in melanoma risk in patients who regularly consumed alcohol. A potential confounding factor is increased high-risk behaviors in alcohol users, including sunburns. Three smaller case–control studies, however, found no association between alcohol consumption and melanoma risk, and one population-level study reported decreased melanoma risk among Swedish women who were also alcoholics [6, 7].

Vitamin D

Polymorphisms of the vitamin D receptor gene may affect melanoma risk. The relationship between serum vitamin D levels, dietary vitamin D supplementation, and melanoma risk, however, remains largely uncertain. Observational studies investigating vitamin D status and melanoma risk provide conflicting results. Two large, prospective cohort studies reported an increased melanoma incidence in patients with higher serum vitamin D levels. Another nested case–control study found no association between serum vitamin D levels and melanoma risk. In addition, one case–control and another cohort study found no association between dietary vitamin D and melanoma risk, while others reported an inverse relationship. Moreover, multiple case–control studies have reported inverse associations between vitamin D levels and poorer melanoma prognosis – namely, an increased Breslow thickness and more advanced stage. Earlier metastatic disease occurred in patients with low serum vitamin D levels, whereas higher vitamin D levels were independently protective against melanoma relapse and death. An RCT found no significant difference in incident melanoma rates in the intervention group (calcium plus 400 IU vitamin D daily) compared with a placebo group. Interestingly, in high-risk patients with a history of NMSC, supplementation resulted in a significantly lower melanoma risk, suggesting a potential role for vitamin D supplementation in this population [63, 64].

Vitamin E

Multiple studies found no association between vitamin E and melanoma risk. Other studies have suggested inverse correlations between melanoma incidence and serum and diet vitamin E levels, supporting a protective role. However, an RCT reported no differences in melanoma incidence in patients receiving long-term vitamin E supplementation (400 IU/day) compared with controls. The safety of vitamin E supplementation is also unclear, since increased all-cause mortality was found in patients receiving high-dose (400 IU/day) vitamin E [20, 28].

Selenium

Selenium is a trace element and antioxidant that relieves the UV-induced depletion of glutathione peroxidase and appears to induce dose-dependent apoptosis and cell-cycle arrest in human melanoma cell lines. In animal studies, oral selenium supplementation resulted in decreased melanoma tumor growth and reduced pulmonary and brain metastases in mice. Human studies, however, are conflicting. In one case–control study, increased environmental exposure to selenium yielded a nearly fourfold greater melanoma incidence than in unexposed controls. Other studies found no significant relationship between selenium levels and melanoma risk. Conversely, metastatic melanoma patients in a case–control study were found to have significantly lower selenium levels than controls [68].

Green Tea Polyphenols

Polyphenols found in green tea, including epigallocatechin-3-gallate (EGCG), possess antioxidant, anti-inflammatory, immunomodulatory, anticarcinogenic, proapoptotic, and photoprotective properties. ECGC inhibits melanoma cell invasion and migration. In addition, green tea supplementation during interferon therapy decreases melanoma cell growth in mice, suggesting its possible use as a treatment adjunct. Despite these promising cell and animal studies, a prospective cohort study was unable to find a significant association between tea consumption and melanoma incidence [7].

Resveratrol

Resveratrol is a naturally occurring polyphenolic compound found in grapes, red wine, some berries, and peanuts. Resveratrol and its chemical analogs have photoprotective, antioxidant, anti-inflammatory, and anticarcinogenic capabilities. The introduction of resveratrol in cell cultures and topical application in human skin resulted in increased cell survival, decreased production of reactive oxygen species, and diminished clinical erythema after UV irradiation. Resveratrol induces the apoptosis of human melanoma cells and promotes cell-cycle arrest. In addition, resveratrol may have a role in metastatic disease, because it possesses antiangiogenic properties and inhibits hepatic and pulmonary metastases. Resveratrol can be used as an adjunct to chemotherapy, radiation, and interleukin-2 by sensitizing melanoma cells to these treatments and preventing toxic endothelial cell injury. Although population-level human RCTs are still lacking, one observational study reported decreased skin toxicity in breast cancer patients being treated with external beam radiation after supplementation with a mixture of vitamins and antioxidants, including resveratrol [7].

Lycopene

Lycopene is a carotenoid found in red fruits and vegetables. It is a potent antioxidant and free radical scavenger that protects against UV photodamage. In animal and human cutaneous models, topical application of lycopene before UV irradiation decreases the inflammatory response, diminishes the generation of matrix metalloproteinases, increases the mean erythema dose, and preserves DNA integrity and normal cell proliferation. Similarly, oral lycopene supplementation decreases toxicity from external beam radiation in patients with breast cancer. Finally, lycopene inhibits platelet-derived growth factor BB and melanoma-induced fibroblast migration, which are known to facilitate metastatic disease. From an epidemiologic perspective, the association between lycopene and melanoma risk is unclear. Three case–control studies found no significant association between serum lycopene levels and the risk of subsequent melanoma. When dietary

lycopene intake was stratified into quintiles, however, one case–control study found that patients in the highest quintile had a significantly lower melanoma risk [7, 28].

Skin Manifestations

Basal Cell Carcinoma

The characteristic features of BCC include the following: waxy papules with central depression, pearly appearance, erosion or ulceration, bleeding (especially when traumatized), crusting, rolled (raised) border, translucency, surface telangiectasia, and slow growth (0.5 cm in 1–2 years) [68].

BCC occurs mostly on the face, head (including scalp), neck, and hands. It rarely develops on the palms and soles. BCC usually appears as a flat, firm, pale area that is small, raised, pink or red, translucent, shiny, and waxy, and the area may bleed following minor injury. BCCs may have one or more visible and irregular blood vessels, an ulcerative area in the center that often is pigmented, and black-blue or brown areas. Large BCCs may have oozing or crusted areas. The lesion grows slowly, is not painful, and does not itch [68].

Squamous Cell Carcinoma

Approximately 70% of all SCCs occur on the head and neck, most frequently involving the lower lip, external ear and periauricular region, or forehead and scalp. The classic presentation of SCC is that of a shallow ulcer with heaped-up edges, often covered by a plaque. Of course, the presenting appearance of each SCC varies according to the site and extent of disease [68].

Melanoma

Clinician and patient education regarding the warning signs of early melanoma has been achieved successfully through the use of the ABCDE criteria for a changing mole, which are as follows [68]:

- Asymmetry: half the lesion does not match the other half
- Border irregularity: the edges are ragged, notched, or blurred
- Color variegation: pigmentation is not uniform and may display shades of tan, brown, or black; white, reddish, or blue discoloration is of particular concern
- Diameter: a diameter greater than 6 mm is characteristic, although some melanomas may be smaller in size; any growth in a nevus warrants an evaluation
- Evolving: changes in the lesion over time are characteristic; this factor is critical for nodular or amelanotic (nonpigmented) melanoma, which may not exhibit the ABCD criteria above

Complementary Examinations

The essential examination is skin biopsy to confirm the diagnosis of skin cancer and serum 25(OH)D.

Therapeutic Approach

A specific diet should not be recommended for skin cancer prevention, because studies have presented conflicting results [14, 68] (Table 38.1).

Skin Infection

Nutritional Correlation

Vitamin D

Recently it has been shown that vitamin D represents a direct regulator of antimicrobial innate immune responses. The innate immune system of mammals provides a rapid response to repel assaults from numerous infectious agents including bacteria, viruses, fungi, and parasites. A major component of this system is a diverse combination of cationic antimicrobial peptides (AMPs) that include the α- and β-defensins and cathelicidins. Because bacteria have difficulty developing resistance against AMPs and are quickly killed by them, this class of antimicrobial agents is being commercially developed as a source of peptide

antibiotics. Recent studies have shown that cathe-licidins, in addition to being antimicrobial, are multifunctional proteins with receptor-mediated effects on eukaryotic cells and activity in chemo-taxis, angiogenesis, and wound healing. In the skin, there is low constitutive expression of hCAP18 in the basal layer of keratinocytes but rapid upregulation upon inflammation and injury. Because AMPs serve a role in host defense and may act as mediators of other biological processes, their expression is tightly regulated. Moreover, vitamin D induces increases in antimicrobial pro-teins and secretion of antimicrobial activity against pathogens including *Pseudomonas aeruginosa*. Some studies have demonstrated the link between vitamin D and Toll-like receptors, cathelicidin production, and increased susceptibility to bacte-rial infections. In addition, vitamin D stimulates the synthesis of proteins such as filaggrin, which is essential to the formation of stratum corneum. Thus, vitamin D deficiency may exacerbate AD by altering the skin barrier and undermining the immune system, leading to a subsequent increase in the risk of infections [6, 7, 14] (Chart 38.1).

Obesity

Obese patients easily become overheated and sweat more profusely because of the thick layers of subcutaneous fat, thus exaggerating areas of inflammation and rashes.

It is widely accepted that *C. albicans* infection is more prevalent in patients with diabetes mellitus because these patients have a significantly higher pH in intertriginous areas. This may be a factor that promotes the susceptibility of patients with diabetes mellitus to *Candida* infection of the skin. Nevertheless, it is noteworthy that some studies have reported that despite half of the patients stud-ied having diabetes mellitus, intertrigo was not a frequent finding. However, the statistical linear trend showed a strong predisposition to intertrigo according to the degree of obesity [36, 53].

Skin Manifestations

Common locations of candidiasis include the genitocrural, subaxillary, gluteal, and submam-mary areas, and between the abdominal skin-

folds. Typically such patients present scaling, erythema with macules, papules, and/or satellite pustules. They may complain of itching or burn-ing over the affected area. *C. albicans* has a pre-dilection for colonizing macerated skinfolds. Accordingly, intertrigo in its various forms is the most common clinical presentation of candidiasis on the skin [69].

Impetigo is the most common bacterial infec-tion. This acute, highly contagious infection of the superficial layers of the epidermis is primar-ily caused by *Streptococcus pyogenes* or *S. aureus*. Impetigo is classified as either nonbul-lous (about 70% of cases) or bullous [69].

Complementary Examinations

Gram stain and culture of the pus or exudates from skin lesions, and serum 25(OH)D.

Therapeutic Approach

There is convincing evidence that vitamin D directly regulates AMP gene expression in humans, revealing the potential of these com-pounds for the treatment of opportunistic infec-tions [14, 64] (Table 38.1).

The statistical linear trend showed a strong predisposition to infection according to the degree of obesity. Hence, weight loss is the best means of reducing this predisposition [36, 53].

Urticaria

Nutritional Correlation

Many patients with chronic urticaria attribute their symptoms to food intolerance. Food prod-ucts including wheat, dietary fats, and alcohol are thought to play a role in the development of urti-carial lesions [20, 28].

Pseudoallergens

The term pseudoallergen is used to describe a stimulus that provokes histamine or cutaneous mast cell degranulation via a nonimmunologic

pathway (i.e., not IgE mediated). It has been estimated that 1–3% of patients with chronic urticaria exhibit pseudoallergic reactions. Pseudoallergens include, but are not limited to, artificial preservatives and sweeteners, food dyes, aromatic compounds in some natural foods (e.g., tomatoes, herbs), and phenolic substances (salicylic acid, *p*-hydroxybenzoic acid, anethole, ethyl vanillin, citron oil, and orange oil). Although the existence of pseudoallergens is not universally accepted and remains somewhat controversial, pseudoallergens are postulated to induce or aggravate chronic urticaria in a subset of patients [20, 59].

Pseudoallergen-induced urticaria may be related to increased gastroduodenal permeability or altered histamine metabolism. Several studies found that pseudoallergen-free diets improved symptoms in a small subset of patients with chronic urticaria, including those who were unresponsive to standard treatments [59].

Because patients differ in terms of the specific pseudoallergens that trigger urticaria, symptom diaries and oral food challenges are useful in determining whether an ingredient or additive plays an exacerbating role. Interestingly, after several months of dietary avoidance many patients can return to a normal diet without experiencing reoccurrence of urticaria. In contrast to medications, a pseudoallergen–free diet may be curative rather than symptom suppressing [20, 28, 59].

A variety of artificial pseudoallergens has been identified, primarily in the form of preservatives and dyes (tartrazine, sodium benzoate, BHT, Sunset Yellow FCF, Food Red 17, Amaranth, Ponceau 4 R, Erythrosine, Brilliant Blue FCF) as well as additives such as monosodium glutamate and sweeteners (saccharine). Both humoral and cell-mediated immune responses have been shown to be responsible for inciting urticarial lesions. Artificial food additives are thought to play a greater role in chronic urticaria afflicting children, whereas natural pseudoallergens evoke more sensitivity among adults. Although artificial pseudoallergens have received significant attention, there also is increasing awareness of the role of natural pseudoallergens in urticaria. These include natural food dyes, such as annatto extract, salicylates, and aromatic compounds, found in high concentrations in several types of fruits, vegetables, and spices. Unlike artificial pseudoallergens, quantities of naturally occurring pseudoallergens are difficult to estimate as they vary considerably in each fruit or vegetable depending on its type, age, and place of origin. They include phenolic substances such as *p*-hydroxybenzoic acid, cumaric acid, salicylic acid, natural flavors, and ethereal oils. Natural pseudoallergens pose a challenge in the management of urticaria because of the difficulty of avoiding all foods containing these ingredients. Testing to determine the natural pseudoallergens to which the patient is sensitive can help in developing a dietary regimen. Although complete elimination is not possible, lowering the consumption of certain natural pseudoallergens may help to ameliorate symptoms of urticaria [28, 59].

Gluten

Because some cases of urticaria are immune mediated, it is not surprising that an association between chronic urticaria and celiac disease has been proposed. Chronic urticaria may be a cutaneous manifestation of celiac disease. Alternatively, increased mucosal permeability in celiac disease can facilitate the passage of antigens, provoking urticaria symptoms. In addition, the inflammatory response generated in celiac disease may trigger production of anti-IgE receptor antibodies that inappropriately activate mast cells; this pathogenic mechanism has been implicated in 35–40% of cases of chronic urticaria. In addition, there are several case reports of resolution of urticaria with concomitant celiac disease soon after initiating a gluten-free diet [20, 28, 59].

Vitamin D

Compared with unaffected controls, patients with chronic urticaria have significantly lower serum vitamin D levels. Some studies have shown complete clinical resolution of urticaria after vitamin D supplementation. An RCT found that high-dose (4,000 IU/day) vitamin D supplementation improves chronic urticaria regardless of baseline vitamin D status [14, 59] (Chart 38.1).

Wheat

Wheat-dependent exercise-induced anaphylaxis is part of a larger entity of food-dependent, exercise-induced anaphylactic reactions, whereby ingestion of a specific food before physical exercise triggers anaphylaxis. Symptoms include pruritus, urticaria, angioedema, dyspnea, hypotension, and shock, which are indistinguishable from those in classic IgE-mediated anaphylaxis. Common triggering foods include celery, shellfish, peanut, tree nuts, and tomato. A frequent cause, however, is wheat. The water-salt-insoluble component of wheat, gliadin, is rich in glutamine residues and becomes modified by the intestinal enzyme, tissue transglutaminase (tTG). Exercise, a physical stressor, may be a potential activator of tTG. Exercise may also increase intestinal allergen absorption, provoke abnormal responses of the autonomic nervous system, or lower the threshold for IgE-mediated mast cell degranulation [28, 59].

Alcohol

Alcoholic beverages are a known cause of several hypersensitivity reactions, including the "flushing syndrome" seen in patients of Mongolian descent or drug-induced by disulfiram, from an elevated acetaldehyde level; asthma exacerbation; exercise-induced anaphylaxis; and urticaria and angioedema. Although urticaria is a rare reaction, there are several theories regarding its mechanism, including altered prostaglandin metabolism, acetaldehyde-induced hapten formation and release of IgE, and a non-IgE-mediated anaphylactic release of histamine. Total serum IgE levels are increased with alcohol consumption. In addition, individuals who regularly consume alcohol have increased sensitization to dust mites, grass pollen, and food allergens [20, 59].

Probiotics

Intestinal microbiota plays an important role in the development of food allergy and food allergen-associated urticaria. Probiotics, when given in infancy, may address the root cause by preventing allergic sensitization to foods, which can subsequently manifest with urticaria [20].

Skin Manifestations

Urticaria is characterized by transient, erythematous, raised skin lesions that are typically intensely pruritic. Although usually not life threatening, the skin disorder is difficult to manage and often impairs the quality of life. The classification of urticaria is based on the duration of the symptomatic episode; it is defined as acute if whealing persists for less than 6 weeks and as chronic if it persists for 6 weeks or longer. The pathogenesis is not yet fully understood, and a triggering factor is only identified in 10–20% of cases [59].

Complementary Examinations

In chronic urticaria patients, it is mandatory to perform complementary examinations to exclude diseases that could be associated or be the cause of the symptoms. The following serum tests are recommended: complete blood count, erythrocyte sedimentation rate, C-reactive protein, liver function tests, thyroid-stimulating hormone, anti-thyroid peroxidase antibodies, antinuclear factor, complement, protein electrophoresis, cryoglobulins, 25(OH)D, total IgE, and serology to hepatitis and HIV infections. Urinalyses with culture and stool test are also important.

Therapeutic Approach

Interventional trials support the benefit of a pseudoallergen-free diet and vitamin D supplementation for patients with chronic urticaria. Given its low cost and safety profile, a pseudoallergen-free diet can be recommended to a subset of chronic urticaria patients. Before issuing a recommendation for vitamin D supplementation, appropriate dosage and treatment duration should be determined through RCTs [20, 28, 59].

A gluten-free diet may ameliorate chronic urticaria symptoms in patients who have concomitant celiac disease. However, there are currently no RCTs to support this recommendation [20, 59] (Table 38.1).

Vitiligo

Nutritional Correlation

Vitamin B12

In the literature, studies of the use of vitamin B12 or cobalamin in the treatment of vitiligo have yielded contradictory results. This makes it difficult to determine when cobalamin deficiency should be investigated in patients presenting with vitiligo. Some studies found that vitiligo patients had higher homocysteine and hemoglobin levels and lower levels of vitamin B12 and holotranscobalamin, which is considered the earliest marker of deficiency. The authors suggested that the association may be due to a common genetic background among patients with cobalamin deficiency, hyperhomocysteinemia, and vitiligo. In a study of patients with vitiligo, most patients experienced repigmentation with prolonged oral folic acid and ascorbic acid and parenteral vitamin B12 supplementation. However, another study compared UVB therapy alone and UVB therapy with vitamin B12 and folic acid, and found no significant difference in the repigmentation rates between the two groups [70, 71].

Vitamin D

Low levels of vitamin D have been observed in vitiligo patients and in patients with other autoimmune diseases. Therefore, the relationship between vitamin D and vitiligo needs to be investigated more thoroughly. Vitamin D increases melanogenesis and the tyrosinase content of cultured human melanocytes by its antiapoptotic effect. However, a few growth-inhibitory effects on melanocytes were also reported. Vitamin D regulates calcium and bone metabolism, controls cell proliferation and differentiation, and exerts immunoregulatory activities. Vitamin D exerts its effect via a nuclear hormone receptor for vitamin D and decreases the expression of various cytokines that cause vitiligo [72].

Phyllanthus emblica, Vitamin E, and Carotenoids

Phyllanthus emblica, vitamin E, and carotenoids are compounds showing antioxidant, anti-inflammatory, and repigmentation effects. A study compared two groups of patients, one treated with one tablet of an oral supplement containing *P. emblica* (100 mg), vitamin E (10 mg), and carotenoids (4.7 mg) three times a day for 6 months (group A) and a control group, which instead was not treated with antioxidants (group B). Both groups were simultaneously treated with a comparable topical therapy and/or phototherapy. After a 6-month follow-up, a significantly higher number of patients in group A had a mild repigmentation on the head/neck regions and on the trunk. The number of patients who presented no repigmentation in head/neck, trunk, and upper and lower limbs was significantly higher in group B. Moreover, group B patients showed higher signs of inflammation, more rapid lesion growth, greater worsening of the disease, and more erythema, whereas group A patients showed a greater disease stability. These results suggest that the use of antioxidant supplementation in patients with vitiligo might represent a valuable instrument, but further research is needed [20, 28].

Gluten

In celiac disease and for associated DH, the elimination of gluten has been associated with significant improvement. Since celiac disease is commonly associated with vitiligo, in patients who have both conditions eliminating gluten will be particularly advantageous.

Rechallenging with gluten would be more conclusive and has been recommended, although it is not an option that patients are always willing to pursue.

There is one documented case of rapid repigmentation of acrofacial vitiligo involving the elimination of gluten in an adult patient without concomitant celiac disease. This novel approach certainly needs to be further explored [20, 28].

Iron

Iron is involved in the antioxidant system, and large amounts of iron are sequestered by ferritin. Ferritin is an important acute-phase reactant whose serum level is increased in some autoimmune disorders. Only one report has investigated

serum ferritin levels in vitiligo. Immune-mediated and free-radical damage to melanocytes is the most probable pathologic mechanism for vitiligo. Although the exact immunopathogenic mechanisms are still unknown, the autoimmune pathogenesis of vitiligo is supported by data from the literature: detection of circulating antibodies to melanocytes and circulating melanocyte specific cytotoxic T cells in vitiligo patients, and the association with other autoimmune disorders and vitiligo [20, 70].

Skin Manifestations

Vitiligo manifests as acquired white or hypopigmented macules or patches. The lesions are usually well demarcated, and round, oval, or linear in shape. The borders may be convex [1]. Lesions enlarge centrifugally over time at an unpredictable rate and range from millimeters to centimeters in size. Initial lesions occur most frequently on the hands, forearms, feet, and face, favoring a perioral and periocular distribution. Vitiligo lesions may be localized or generalized, with the latter being more common than the former. Localized vitiligo is restricted to one general area with a segmental or quasi-dermatomal distribution. Generalized vitiligo implies more than one general area of involvement. In this situation, the macules are usually found on both sides of the trunk, either symmetrically or asymmetrically arrayed [73].

Complementary Examinations

Serum vitamin B12, iron, and 25(OH)D level are recommended.

Therapeutic Approach

There are few reports in the published literature of dietary intervention as a treatment modality for vitiligo. While there may be a relationship between nutritional elements and vitiligo, further research is needed to elucidate the nature of the association and the clinical application [14, 73, 74] (Table 38.1).

Dermatosis and Bariatric Surgery

Metabolic and nutritional diseases are among the main complications of bariatric surgery (BS). These are secondary to decreased oral intake, as well as alterations in food absorption in the stomach and areas of the small intestine. Patients may also experience diarrhea, nausea, and vomiting, which may trigger fluid and electrolyte imbalance that may persist for more than 5 years after surgery. Typically, patients after undergoing BS show decreased absorption of liposoluble vitamins, iron, vitamins B12, A, D, E, and K, folic acid, and thiamine. Studies have suggested that gastric bypass surgery in patients with psoriasis can result in complete remission. The improvement starts immediately after surgery, before any weight loss. Similarly, in the literature there are case reports of remission of necrobiosis lipoidica after BS. However, there is still much to be elucidated about the true nature of the mechanisms leading to this process [14].

Glossary

Antimicrobial peptides A growing class of natural and synthetic peptides with a wide spectrum of targets including viruses, bacteria, fungi, and parasites.

Cathelicidin Related antimicrobial peptides found in lysosomes of macrophages and polymorphonuclear leukocytes, and keratinocytes. Cathelicidins have a critical role in innate immune defense against invasive bacterial infection.

Essential fatty acid An unsaturated fatty acid that is essential to human health but cannot be manufactured in the body.

Pseudoallergen An antigen that causes allergy-like symptoms, but without identifiable sensitization of the immune system.

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Smoking, Alcoholism, and Use of Illicit Drugs

39

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Key Points
- Smoking tobacco is associated with malignancies, besides the worsening of postsurgical scarring process and skin aging
- Smoking is related to the triggering and worsening of dermatoses, such as Buerger's disease, lupus, psoriasis, and hidradenitis suppurativa
- Cutaneous manifestations of alcoholism include those associated with endocrinologic changes, such as hypogonadism and gynecomastia, nutritional deficiencies of the complex B vitamins, and signs of hepatopathy
- Alcoholism is associated with diseases such as psoriasis, porphyria, seborrheic dermatitis, rosacea, urticaria, and contact dermatitis
- Drug addiction is characterized by recurrent use, and causes severe physical and social consequences
- In addition to the vasculopathy caused by levamisole-contaminated cocaine, this drug produces laboratory changes that may clinically mimic some rheumatologic diseases

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Tobacco Smoking

Epidemiology

Smoking is one of the main modifiable risk factors for mortality, with a prevalence of 20–30% in developed countries and 10–50% in developing countries [1]. It decreases life expectancy by15 years, and accounts for death in one-third of tobacco users. The prevalence is higher in men, blacks, persons with less education, and the impoverished, and it continues to grow, mainly among young women.

Worldwide, more than 5.4 million deaths annually are associated with tobacco smoking, besides tuberculosis, HIV/AIDS, and malaria [1]. Tobacco consumption is related to cardiovascular

diseases, chronic bronchitis, lung emphysema, and many dermatologic diseases [2]. Approximately 40% of neoplasias are associated with tobacco smoking, including those occurring in the lungs, mouth, pharynx, larynx, esophagus, cervix, kidney, and bladder.

Etiopathogenesis

Tobacco smoking comprises a volatile or gaseous phase and a particulate or solid phase. The solid phase has about 3,500 elements, including nicotinic alkaloids [2]. There are many mutagens and carcinogens, notably polycyclic aromatic hydrocarbons, nitrosamines, and heterocyclic amines [3] (Table 39.1).

The skin is an organ exposed to cigarette smoke, both directly through contact with environmental smoke and indirectly through toxic substances that travel from the inhaled smoke into the bloodstream [2]. Dysfunction of the

microvasculature occurs as flow decreases at 30–40%, carboxyhemoglobin increases, oxygen decreases, neovascularization decreases, fibroblast activity decreases, vitamin C decreases, and platelet aggregation and blood viscosity increase.

Cutaneous Manifestations

Tobacco smoking may affect many chronic dermatoses and their treatment. Smoking cessation or decrease can be an effective therapeutic measure. Conversely, nicotine has been effective as monotherapy in some dermatologic conditions (there are cutaneous receptors of acetylcholine of nicotinic class). Thus, smoking can be related to the worsening or the triggering of dermatoses, and there are reported improvements of some dermatoses (Table 39.2).

Obliterans Thromboangiitis

More than 90% of patients with ulcers resulting from Buerger's disease are tobacco smokers. While most tobacco components can induce vasoconstriction and exacerbate the disease, nicotine use can be a prospective therapeutic option. There are reports of successful use of nicotine gum [3].

Cutaneous and Systemic Lupus Erythematosus

The relationship between tobacco smoking and systemic lupus erythematosus has been researched in many studies, and some authors have noticed a positive relationship while others have not. A recent retrospective study assessed the relationship between tobacco smoking and lupus, reaching the conclusion that the discoid and tumid variant was clearly associated with smoking, whereas the systemic form did not show such an association [4]. Besides displaying more disease activity, treatment with antimalarial drugs showed decreased efficacy in tobacco-smoking patients [5].

Carcinogenesis

Epidemiologic studies have shown correlations among tobacco smoking and the incidence and aggressiveness of certain types of skin cancer.

Table 39.1 Toxic components of tobacco

Phase	Components
Solid	Nicotine
	Phenol
	Catechol
	Quinoline
	Aniline
	Toluidine
	Nickel
	N-Nitrosodimethylamine
	Benzopyrenes
	Benzanthracene
	2-Naphthylamine
Gas	Carbon dioxide (CO_2)
	Carbon monoxide (CO)
	Hydrogen cyanide (HCN)
	Nitrogen oxide (NO_2)
	Acetone
	Formaldehyde
	Acrolein
	Ammonium
	Pyridine
	3-Vinylpyridine
	N-Nitrosodimethylamine
	N-Nitrosopyrrolidine

Table 39.2 Relation between tobacco/nicotine and skin manifestation

Skin manifestation	Association	Observations
Aberrant wound healing	↑	Unaesthetic scars, infections, suture failure; affects results of flaps and full-thickness grafts
Buerger's disease	↑	90% of patients with ulcerations are smokers
Lupus erythematosus	↑	Discoid and tumid variants
Lupus erythematosus variant systemic	–	Treatment with antimalarial drugs has limited effectiveness in smokers
Squamous cell carcinoma	↑	Particularly associated with increased risk of penile carcinoma and cancers of the vulva, cervix, anus, and oral cavity
Keratoacanthoma	↑	
Malignant melanoma	?	Effect on the incidence is not established; prognostic implications
Psoriasis	↑	Dose-response relationship with the number of cigarettes smoked per day, particularly in the pustular form
Hidradenitis suppurativa	↑	
Acne vulgaris	?	
Atopic dermatitis	?	
Contact dermatitis	?	
Skin aging	↑	Smoker's face; Favre–Racouchot syndrome
Oral melanosis	↑	Active smoking sign
Stomatitis by nicotine or palate leukokeratosis	↑	Active smoking sign
Yellowish discoloration of the facial hair, nails, and fingers	↑	Active smoking sign
Harlequin nails	↑	Smoking cessation sign
Aphthous ulcers	↓	
Behçet's disease	↓	
Pemphigus vulgaris	↓	
Pyoderma gangrenous	↓	
Herpes simplex	↓	Reduces the intensity and frequency of episodes
Rosacea	↓	
Dermatitis herpetiformis	↓	

↑ increased incidence and/or exacerbation; ? controversial reports; – no relation; ↓ decreased incidence and/or improvement

Smoking is an independent risk factor for the development of squamous cell carcinoma (SCC). Particularly, it is associated with increased risk for penile, vulval, cervical, and anal carcinoma, and oral cancer [3]. Regarding the latter, there is greater risk in women smoking unfiltered cigarettes.

In addition, excessive alcohol consumption has a synergistic effect if combined with cigarette use, thus significantly increasing the risk for the development of mouth carcinoma [2].

Keratoacanthoma
There is a connection between keratoacanthoma and tobacco smoking. In a case-control study of 78 patients the smoking prevalence was 69.2% in the group of keratoacanthoma cases, compared with 21.6% in the control group [1].

Malignant Melanoma
Many research studies that fail to provide enough evidence to establish the influence of tobacco smoking on melanoma incidence. However, prognostic implications have been verified [2]. The proportion of male smokers free from the disease 5 years after the diagnosis was significantly smaller than in nonsmoking men. Moreover, smokers were prone to display early metastases and visceral metastases within the first 2 years after the diagnosis [3].

Postsurgical Complications

Cutaneous complications after surgeries include development of unaesthetic scars, infections, suture failure, and harmful outcomes of total-thickness cutaneous flaps and grafts.

These risks were shown to be dependent upon the amount of cigarettes smoked per day. Although the minimum period of tobacco avoidance is yet to be established, some experimental studies and clinical observations suggest that cessation of tobacco consumption 2 weeks before and 1 week after surgery tends to minimize complications of surgical wounds [9].

Other Dermatoses

Psoriasis

Tobacco consumption is associated with the risk of developing psoriasis, and there is a dose-reaction relationship with the amount of cigarettes smoked per day [3], particularly with the pustular form (Fig. 39.1), when the acrosyringium is the inflammation target. Cessation of tobacco consumption leads to a significant improvement, with fewer pustules, and less erythema and scaling. It is known that 95% of these patients are smokers, most of them being heavy smokers [1].

Hidradenitis Suppurativa

Hidradenitis suppurativa (HS, Fig. 39.2), or inverted acne, is epidemiologically associated with tobacco smoking. Chemical components in tobacco activate keratinocytes, fibroblasts, and two kinds of receptors, the acetylcholine nicotinic
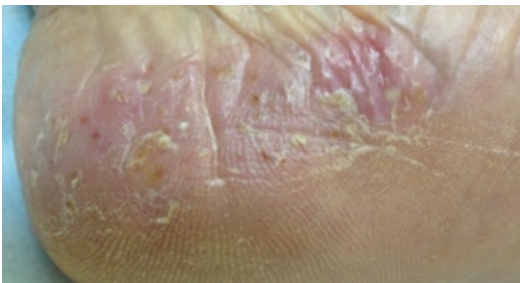
Fig. 39.1 Pustular psoriasis

Fig. 39.2 Hidradenitis suppurativa

receptors and the aryl hydrocarbon receptors. These are found in the keratinocytes. Acanthosis, hyperplasia of the infundibular epithelium, and excessive cornification are factors implicated in HS pathogenesis [6].

Acne

Some reports showed a dose-dependent linear relationship between prevalence and severity of acne vulgaris and cigarette consumption, whereas others showed no such association [3].

Atopic Dermatitis

Although tobacco smokers show a total immunoglobulin E (IgE) serum level significantly higher compared with nonsmoking subjects, reports are conflicting regarding effects of tobacco smoking on atopic patients [3]. Mills et al. did not find differences in smoking prevalence between patients with atopic dermatitis and a control group [2].

Contact Dermatitis

There is some controversy regarding the association of the smoking habit and contact dermatitis [1]. Linneberg et al. found a significant association between tobacco smoking and a positive result of contact test for nickel and allergic contact dermatitis [2]. The contact test has to be considered in smoking patients who display hand, face, and neck dermatitis. Besides the standard series, in these cases specific allergens should also be tested, including cocoa, menthol, licorice, formaldehyde, and cigarette components [1]. Nicotinic patches can cause allergic contact dermatitis, or by primary irritation on the application sites, with nicotine being the main involved allergen [3]. A prospective cohort study reported increased severity of occupational hand dermatitis in tobacco smokers [7], but there is no

verified association between hand dermatitis and tobacco consumption in any present systematic review [8].

Cutaneous Aging

Tobacco smoking is a significant accelerator of the aging process through multiple mechanisms [1, 3]: free radical development, decrease and increased breakdown of type I and type II collagen synthesis, increased elastic fibers resulting in degradation of elastic material, decreased susceptibility threshold to ultraviolet effects, decreased cutaneous turgor, and induction of metalloproteinase synthesis.

There are characteristic cutaneous signs (Fig. 39.2) related to smoking habit, including the following possibilities [3, 10]:

– "Smoker's face": wrinkles, contour prominence, atrophic greyish aspect, and plethoric frame
– Favre–Racouchot syndrome: multiple and large open comedones located in the lateral and inferior orbital region, consistently associated with long-term solar exposure.

Oral Melanosis

One-third of tobacco smokers display oral pigmentation [3], with melanin gingival pigmentation resulting from increased melanin in the epidermal basal layer [1].

Nicotinic Stomatitis/Palatal Leukokeratosis

This is an area with multiple umbilicated pustules at the two-thirds posterior areas of the hard palate that represent inflamed salivary glands. The condition is more commonly seen in pipe smokers [2].

Yellow Discoloration

Yellow discoloration of mustache, nails, and fingers as side effects of smoking tobacco.

Harlequin Nails

This occurs when tobacco consumption stops and a demarcation arises between a distal pigmented nail and a growing nail [3].

Protective Effects of Tobacco Smoking

A potentially low incidence of some dermatoses in tobacco smokers has been reported. Perhaps because tobacco increases oral mucosa keratinization (among other factors), there are some "negative" associations: (1) ulcers resulting from Behçet's disease apparently improve with tobacco smoking and nicotine; (2) there is a decreased risk for new lesions of pemphigus and pyoderma gangrenosum; (3) tobacco smoking inhibits herpes simplex replication and decreases its cytolytic effect, thus reducing the intensity and frequency of new episodes (but, since the viral oncologic activity is inversely related to its cytolytic activity, tobacco smoking can function as a cancer factor); (4) lower incidence of rosacea among tobacco smokers may result from vasoconstrictive effects; (5) the incidence of positive antiendomysial antibodies among newly diagnosed adults with celiac disease (dermatitis herpetiformis) is smaller in tobacco smokers than in nonsmokers [3].

Alcoholism

Epidemiology

Substance abuse including alcohol and drugs is defined by the American Association of Psychiatry as a maladaptive pattern of substance use clinically leading to significant harm or suffering expressed by one or more than one of the following signs within 12 months:

– Recurrent use resulting in damage,
– Recurrent use in physically dangerous situations,
– Associated legal problems, and
– Recurrent use despite the consequences [11].

Alcohol consumption has an estimated prevalence of 2 billion users and harbors cultural, social, and religious aspects. Its early use is a risk factor for future abuse. It represents up to 4% of deaths in general, and is twice to three times more common in men. Alcohol abuse represents a significant cause of mortality and morbidity and has implications in multiple health conditions [11, 12].

Rehm et al. concluded that ethanol abuse is one of the greatest avoidable risk factors, and actions to reduce the heavy costs associated with ethanol should be urgently implemented [13].

Skin Manifestations

Alcohol is directly toxic to the liver resulting in hepatic steatosis, alcoholic hepatitis, and cirrhosis. Its abuse also accounts for up to 65% of acute and chronic pancreatitis. Although moderate consumption may be protective against coronary disease, heavy consumption can lead to cardiomyopathy, hypertension, arrhythmias, and cerebrovascular hemorrhage. Other medical consequences include increased risk for certain types of cancer, and nutritional deficiencies [14].

Endocrinologic Changes

Hypogonadism
Loss of libido and impotence, testicular atrophy, fertility decrease, and reduced facial hair growth in men.

Hyperestrogenism
Hyperestrogenism consists of gynecomastia, vascular spiders, altered body fat distribution, and loss of body hair. Women seldom show signs of masculinization although they can have mammary atrophy and irregular menses.

Pseudo-Cushing Syndrome
Pseudo-Cushing syndrome may be difficult to distinguish from Cushing syndrome by manifesting full-moon facies, centripetal obesity, loss of proximal muscle mass, buffalo hump, abdominal striae, hypertension, and osteoporosis [14]. Besemer et al. [15] noticed that in most patients biochemical and clinical abnormalities were found, thus mimicking increased activity of the hypothalamic-hypophyseal-adrenal axis. Biochemical changes and regressive hypercortisolism symptoms cannot be normalized unless alcohol consumption is stopped [15].

Nutritional Deficiencies
The cause is probably multifactorial, including inappropriate nutrient ingestion as well as the hepatotoxic effects of alcohol on food metabolism.

Vitamin B1 (thiamine): one of the most commonly seen deficiencies secondary to damaged gastrointestinal absorption. Damaged gastrointestinal absorption presents as cardiac and neurologic complications; patients' skin may appear waxy and their tongue can become thick and reddish.

Vitamin B2 (riboflavin): deficiency results in angular cheilitis, atrophic glossitis, and a facial erythema that resembles seborrheic dermatitis [11].

Vitamin B3 (niacin): pellagra displays a classic tetrad including dermatitis, diarrhea, dementia, and death (if not treated). Dermatitis is characterized by red-chestnut plaques, with eventual vesicles or bullae, on photoexposed skin mainly on the face, arms, and legs (Fig. 39.3). Casal collar is the term used for the lesion plaque around the neck.

Vitamin B6 (pyridoxine): a deficiency also commonly associated with alcoholism, characterized by similar seborrheic dermatitis on the face, neck, shoulders, and perineum. Patients can also show angular stomatitis and glossitis [14].

Vitamin B12 (cobalamin): vitamin B12 deficiency is recognized by hyperpigmentation in "glove" and "boot," whereas folate deficiency can display diffuse hyperpigmentation (Fig. 39.4).
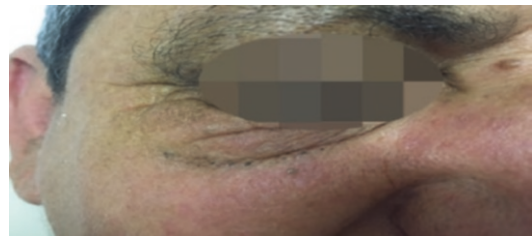
Fig. 39.3 Smoker's face/Favre–Racouchot syndrome

Fig. 39.4 Pellagra

Signs of Alcoholic Hepatopathy

It should be borne in mind that many changes may be secondary to hepatopathy of any etiology and not specific to alcoholic hepatic disease, as shown in Box 39.1.

Psoriasis and Alcohol Use

Many factors are implicated in the pathogenesis of psoriasis, including physical and psychic stress, metabolic factors, tobacco smoking, drugs, infections, and trauma. Extensive evidence shows a link between ethanol abuse and

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Box 39.1 Cutaneous Signs of Hepatopathy

Gynecomastia

Increased parotid

Decreased pili

Palmar erythema (Fig. 39.5)

Telangiectasia

Jaundice

Ungual alterations

Terry nails: two-thirds proximal to the ungual fold are white whereas 2 mm distal are pink. Can be seen in 80% of cirrhotic patients [14]

Hippocratic fingers: alteration of the Lovibond angle between the ungual plaque and the proximal fold greater than 180°, found in 5–15% of cirrhotic patients. It results from increased peripheral blood flow with dilated arteriovenous anastomoses of the fingers and is not due to hypertrophic osteopathy

Transverse bands (Muehrcke): white bands parallel to the lunula separated by a normally pink nail. Frequently associated with hypoalbuminemia [11]

Fig. 39.5 Palmar erythema

psoriasis [12]. Alcohol abuse is a risk factor for psoriasis, both in men and women, given that many of these patients do not display signs of dependence and also show normal results in hepatic function tests [14].

The distribution of cutaneous lesions in the majority of patients tends to be predominantly acral, involving the hand dorsum and the fingers, resembling a pattern seen in immunocompromised patients, such as HIV patients. This element shows the potential role of ethanol in inducing immune dysfunction with negative immunosuppression [11].

It was shown by a research study that daily ingestion of ethanol higher than 80 g resulted in a more severe psoriasis and a lower reaction to treatment [11]. Moreover, the therapeutic options are limited (methotrexate, acitretin) because of the absolute or relative contraindications [12].

Solar Exposition and Alcohol

A transversal research study on alcohol consumption and self-referred sunburns, in which adults were asked about alcohol usage in the previous month and history of sunburns in the previous year, concluded that excessive alcohol consumption is associated with higher rates of sunburns, thus making the risk for cutaneous neoplasias higher. The odds ratio adjusted for prevalence and number of sunburns in ethanol consumers was 1.39 (95% confidence interval 1.31–1.48) and 1.29 (95% confidence interval 1.20–1.38), respectively [16].

Some studies have also suggested that basal cell carcinoma in chronic alcoholics tends to show a more infiltrating pattern, especially in immunosuppressed patients. The tumors are more aggressive and display greater destruction and local recurrence [11].

The main ethanol metabolite, acetaldehyde, has been reported as the greatest influential factor in alcohol-related carcinogenesis and mutagenesis [12].

Alcohol use is associated with a higher risk for scaly cell carcinoma of the oral cavity. Its mechanism is still not clear, although it may be multifactorial because of its immunosuppressive effect associated nutritional deficiencies and synergistic effect related to tobacco consumption.

Alcohol and Other Dermatoses

Porphyria Cutanea Tarda

This is the most prolific porphyria worldwide, and is the only type not exclusively inherited. Alcohol has been shown to be the most significant cause of acquired porphyria cutanea tarda (PCT) [12].

The enzymatic fault that accumulates porphyrins which, in turn, induce photosensitivity, leads to cutaneous manifestations predominantly in photoexposed areas, cutaneous frailty, erosions, blisters with milia, and scar development. Other manifestations include hypertrichosis, mainly on the temples, malar region, and mentum, as well as cutaneous hyperpigmentation (Fig. 39.6).

Affected patients must be instructed to avoid exacerbating factors such as alcohol and solar radiation [11].

Seborrheic Dermatitis

An association between alcohol abuse and seborrheic dermatitis was shown in hepatopathic patients and patients lacking nutrition [11].

Rosacea

Rosacea (Fig. 39.7) is exacerbated by alcohol use. The implicated mechanism is vasodilation and the subsequent temperature rise that leads to

Fig. 39.7 Rosacea

uncomfortable flushing. Long-term alcohol consumption may result in chronic facial erythema and loss of vasoregulatory control [11, 14].

Urticaria

Although rare, there have been reports of occurrence of immediate manifestations of urticaria/angioedema after consumption of small quantities of ethanol.

Urticariform reactions may be limited to the area of direct contact with ethanol, or may occur systemically after contact through percutaneous absorption or ingestion. Specific IgE in cases of suspected ethanol allergy has not been shown [12, 17]. It is not yet clear whether the urticariform reaction can result from the ethanol itself or from additives therein [11].

Systemic Contact Dermatitis

The exact mechanism of systemic contact dermatitis as regards ethanol (SCDE) is uncertain, but probably results from a hypersensitivity reaction (type IV) involving T-cell activation. Ethanol is widely used in topical products such as hand disinfectants and cosmetics, and also as a vehicle for the topical absorption of transdermal medicines.

A case of SCDE was reported after ethanol ingestion by a patient with fixed erythematous and pruriginous rash, with small skin areas spared on the trunk. The patient reported recurrent alcohol ingestion and previous use of transdermal contraceptives, besides sensitivity to the use of topical preparations with alcohol [18].

Discoid Eczema

Discoid or nummular eczema is found with increased frequency in alcohol abusers [14].

Alcohol and Procedures

Alcohol abuse is a significant risk factor for the following surgical complications [14]:

– Infection of the surgical wound: associated with immunosuppression.
– Suture dehiscence: infection associated with nutritional deficiencies can lead to increased dehiscence.
– Bleeding: resulting from compromised platelet function. Coagulopathy due to deficiency of vitamin K may be present in patients with severe hepatic disease.

Alcohol and Drug Interactions

Alcohol may interact with frequently used drugs in dermatologic therapeutics, such as methotrexate and acitretin, given that the concomitant ingestion of acitretin indirectly increases its re-esterification into etretinate. In addition, flushing may occur after administration of certain drugs, such as disulfiram, metronidazole, griseofulvin, and ketoconazole. Pimecrolimus and tacrolimus, calcineurin topic inhibitors used to treat atopic dermatitis, were reported as resulting in intolerance after topical application associated with ethanol ([12], [19]).

Therapeutic Approach

Genetic, environmental, and psychosocial factors may play a relevant role in alcoholism development. Alcoholism is characterized as a chronic, progressive, and potentially lethal disease involving ethanol dependence and multiple organ dysfunction.

Advising patients to quit smoking and alcoholic beverage abuse must be routine with regard to general skin orientations, together with the standard recommendations to decrease sun exposure, because of the significant morbidity/mortality rate associated with such habits.

Heavy advertising and vested economic interest policies regarding tobacco and alcohol consumption exist worldwide. It has been documented that almost all societies where alcohol and tobacco consumption exists report social and health problems associated with abuse.

Ethanol-associated costs reach more than 1% of the gross national product in medium- and high-income countries, with costs related to social damage making up a significant proportion besides health costs [12].

Use of Illicit Drugs and Drug Addiction

Similar to alcohol abuse, drug abuse (drug addiction) is characterized by the recurrent use in the face of the physical and social consequences [11].

The most commonly used illicit substances include marijuana, heroin, cocaine, crack, ecstasy, LSD, methamphetamines, benzodiazepines, anabolic steroids, and GHB (γ-hydroxybutyrate).

Cutaneous manifestations resulting from drugs, though not being pathognomonic, allow the clinician to identify these patients early, and, possibly after excluding many other etiologic factors, the physician can intervene and make referrals to other specialists [20].

Stigmas Related to the Use of Injectable Drugs

A study reported "track marks" or " skin tracks" along the injected veins in 76% of injectable drug users (IDU). These tracks result from phlebitis with postinflammatory hyperpigmentation. Cutaneous granulomas can develop from months to years after exposition. Ulcerations can also develop from the irritating effect of the drug, repeated trauma, or secondary infection [11].

Cutaneous Infections

Cellulitis, abscess, and impetigo are common among IDUs, who can also show necrotizing fasciitis, septic phlebitis, and gangrene. *Staphylococcus aureus* is the most frequently

found agent, followed by the *Streptococcus* species. Infections are the main driver leading drug users to seek medical care [21].

Pruritus and Signs of Excoriation

Pruritus may occur especially with cocaine and methamphetamines. Users can have delusional parasitosis resulting in manipulative lesions and excoriation. Histamine-liberating opioids may cause pruritus that lasts up to 24 h.

Acneiform Eruption

Acneiform eruption has been noted in anabolic steroid abusers.

Damage to the Nasal and Oral Mucosa

Intranasal use of cocaine may result in development of granulomas or septal necrosis, or both. Chronic damage to the nasal mucosa may lead to ischemic necrosis of the cartilage that may evolve to septal perforation.

A well-known effect of methamphetamine abuse is extreme oral disease with dental destruction, known as "meth mouth" [11, 20].

Other Cutaneous and Mucosal Manifestations

The following conditions have been reported to be related to illicit drug abuse: urticaria, angioedema, leukocytoclastic vasculitis, serum disease (amphetamine), maculopapular exanthem, bullous reactions, fixed eruption by drug (heroin), pseudovasculitis/vasculopathy (cocaine: see below), and acute generalized exanthematous pustulosis [11, 20].

Cocaine and Adjuvant Syndrome

It is estimated that more than 17 million people worldwide are cocaine users [22]. Cocaine use causes euphoria and some side effects that include

Table 39.3 Laboratory changes previously described and attributed to the use of levamisole

Laboratory changes described in the literature	
Anemia, leukopenia, or pancytopenia	Rheumatoid factor
Increased creatinine	Anticardiolipin antibodies
Positive P-ANCA and C-ANCA	Hemoglobinuria
Altered FAN and Anti-DNA	Antiphospholipid AB

acute myocardial infarction, tachyarrhythmia, hypertensive crises, and nasal septum perforation, among others [23]. In recent years, changes in patterns of cocaine use have been observed. Purple necrotic lesions on the skin, livedo reticularis, and pancytopenia are often described in association with changes in markers of rheumatologic diseases, such as rheumatoid factor, C-ANCA, P-ANCA, and antinuclear factor (Table 39.3) [24–26]. These changes in clinical and laboratory patterns, which were not previously described among cocaine users, are attributed to levamisole, a medication that has been added to cocaine [25–27].

Cocaine is one of the world's oldest known psychoactive drugs. It is used as a stimulant and is produced from the leaves of the coca plant (*Erythoxylum coca*). Cocaine causes euphoria in the short term. Acute myocardial infarction, hypertensive crisis, heart failure, arrhythmias, and altered mental status are some of the disorders associated with the use of this substance.

In the last decade, cocaine use has been linked to rheumatologic, renal, hematologic, and cutaneous manifestations [24, 25, 28–31]. Over the years the number of reports on this topic has steadily increased. Considering that cocaine has been used for so many years, it was hypothesized that this new profile of diseases found in users was caused by an adjuvant (also called contaminant) which was recently added.

In Brazil and worldwide it is well known that cocaine, as well as other drugs, is often not marketed in its pure form. Many other substances, including talcum powder and medications, were found in analyses of cocaine. In recent decades one of the most frequently added adulterants in street drugs sold as cocaine is the anthelminthic drug levamisole. Approximately 70% of illicit

cocaine consumed in the United States is contaminated with levamisole [32, 33].

Levamisole is an immunomodulatory agent that was used to treat various cancers before being withdrawn from the United States market in 2000 because of adverse effects. Potential complications associated with its use include agranulocytosis, skin necrosis, and pseudovasculitis. Levamisole is currently approved as an anthelminthic agent in veterinary medicine [27].

Levamisole is known to cause purpura in 3% of exposed persons. Patients often present with a rapid and progressive development of livedo reticularis, macules, papules, and purpuric plaques followed by hemorrhagic bullae and necrosis. Classically many authors point out purpuric eruption on earlobes; however, lesions may be found in any area of the body (Figs. 39.8, 39.9, and 39.10). Histologically, some cases reveal leu-

Fig. 39.9 Retiform purpura in a cocaine/levamisole user: reticulated and necrotic center lesion, with "stellate" edges and brighter erythema
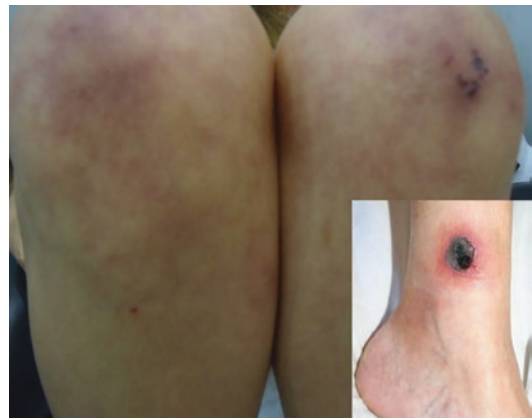
Fig. 39.10 Lesions of livedo reticularis on the knees of a cocaine/levamisole user. Skin necrosis on the right area

kocytoclastic vasculitis and small-vessel thrombosis or medium-sized-vessel vasculitis [34].

In addition to the vasculopathy caused by levamisole-contaminated cocaine, this drug produces laboratory changes that may clinically mimic some rheumatologic diseases. Similar to our own cases, some studies have mainly reported positive anti-neutrophil cytoplasmic antibody (ANCA), which often leads to a false diagnosis of autoimmune vasculitis, including polyarteritis nodosa and granulomatosis with polyangiitis (GPA). In addition to this marker, a few cases of individuals with antinuclear factor, anti-DNA, anti-cardiolipin antibodies, and positive rheumatoid factor have been reported [34, 35]. Positive ANCA induced by drugs

Fig. 39.8 Typical auricular lesion in a cocaine/levamisole user

is common. In the literature there are reports of ANCA positivity with the use of some antibiotics, antithyroid drugs, anti-tumor necrosis factor, and psychoactive agents. Repeated exposure may lead to the formation of autoantibodies in more than 10% of patients, especially after long periods of exposure. The mechanism in the pathogenesis of levamisole/cocaine-induced ANCA positivity is unclear [34, 35].

It has yet to be clarified in the literature whether exposure time or the cumulative dose used is more relevant. The answer is probably multicausal. Depending on genetics and other factors, for some individuals it could be the dose used and for others the exposure time.

Individuals with purpuric lesions, livedo reticularis, acute renal failure, and agranulocytosis with a positive ANCA diagnosis should be excluded from the clinical history of exposure to levamisole and cocaine. Therefore, we recommend the use of ANCA as a diagnostic marker for cocaine use and levamisole. Individuals with these characteristics should be investigated for history of ingested drugs, including cocaine and its derivatives.

The diseases caused by an adjuvant added to cocaine can be grouped into a complex syndrome referred to as autoimmune/inflammatory syndrome induced by adjuvants (ASIA). Four entities are included: (1) postvaccination phenomenon; (2) Gulf War syndrome; (3) macrophagic myofasciitis; (4) siliconosis.

The main environmental factors involved in ASIA are aluminum hydroxide (adjuvant in vaccines), silicone, squalene, and mineral oil used for cosmetic purposes.

Gulf War syndrome is related to multiple vaccinations made in a short time in addition to smoke from oil-well fires or depleted uranium from shells, as well as physical and psychological stress. The majority (95%) of overtly ill deployed Gulf War syndrome patients had antibodies to squalene.

The clinical spectrum of the syndrome that occurs after vaccination include vasculitis, inflammatory myopathy, neurologic syndromes, inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, autoimmune thrombocytopenia, and other nonspecific autoimmune manifestations.

Silicone, a synthetic polymer, is considered to be a biologically inert substance; however, silicone may mediate autoimmune diseases, mainly scleroderma, although controversy about this issue is ongoing.

It can be observed that the syndrome is described with varied clinical and laboratory (scleroderma and macrophagic myofasciitis) or pleomorphic manifestations (vasculitis). The latter is observed in cocaine/levamisole users. Considering that levamisole is an adjuvant to cocaine, we suggest the inclusion of this new entity in the ASIA group.

In conclusion, drug addiction is a risk factor for sexually transmitted diseases, depression, accidental injuries, criminal violence, and domestic abuse. By recognizing cutaneous manifestations of illicit drug use the dermatologist has the opportunity to intervene, and can have a significant impact on the patient's health [21].

Glossary

Acetylcholine Neurotransmitter released by cholinergic neurons responsible for muscle contraction, learning, and memory, whose action is mediated by nicotinic and muscarinic receptors found at the neuromuscular junctions in the central and peripheral nervous system.

Acneiform eruption Dermatosis related to the development of papules and follicular pustules, with or without comedones, connected to predisposing factors or medicines, located in sites that do not usually show acne, or occurring in life stages other than adolescence.

Carboxyhemoglobin Molecule of carbon monoxide linked to a molecule of hemoglobin. Its development is associated with carbon monoxide toxicity.

Carcinogen A substance, situation, or exposition that can damage the genetic material (DNA), thus initiating or stimulating cancer development.

Cheilitis Lip dermatosis resulting from different causes that manifests as erythemas, scaling, vesicles, fissures, tumefaction, nodules, and so forth.

Comedones Solid development in the pilosebaceous follicles resulting from retained sebum produced by the gland due to acroinfundibulum obliteration by focal keratosis.

Cytolytic Related to cell destruction (cytolysis).

Discoid Semiologic description of lesion feature shaped like a disc.

Glossitis Alterations of the tongue mucosa caused by poor nutrition, infections, and physical, chemical, or drug-induced irritation that are manifested by partial or total loss of the filiform papillae, and smooth and red tongue.

Gynecomastia Increased breast tissue, unilaterally or bilaterally, in men.

Jaundice Yellow color of skin, mucosa, and sclera caused by hyperbilirubinemia.

Keratinization Final phase of the keratinocyte differentiation whereby keratin is formed.

Metalloproteinases Zinc-dependent proteinases that show cleavage activity (gelatinolytic) of the matrix and angiogenic and inflammatory activities, synthesized by many cells including fibroblasts and leukocytes.

Mutagenic Physical, chemical, or biological agent which can cause mutation if exposed to one cell, i.e., damage to the DNA that is not repaired and is passed on to the next generations.

Neovascularization Development of new blood vessels. This process can be physiologic or pathologic.

Nummular Semiologic description of lesion feature as "rounded, resembling coin."

Pathognomonic The characteristic and proper sign of a disease.

Plethoric Red coloration through vascular engorgement in polycythemic patients; increased blood volume.

Rhytids Skin lines and depressions resulting from facial, neck, hand, and arm aging, commonly known as wrinkles.

Steatosis Tissue fat accumulation.

Stomatitis Dermatosis of mucosa of the buccal cavity of multiple etiology, such as infections and nicotine.

Telangiectasia Dilation of dermal small blood vessels.

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Hepatitis

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Gislaine Silveira Olm

Key Points
- The infection caused by hepatitis B and C and its complications are a global health problem
- Several extrahepatic syndromes are associated with these chronic viral infections, including significant morbidity and mortality
- Serum sickness and polyarteritis nodosa are the main cutaneous manifestations associated with infection caused by hepatitis B virus
- Cutaneous manifestations related to infection with hepatitis C include mixed cryoglobulinemia, porphyria cutanea tarda, and lichen planus
- Skin adverse reactions, both local and diffuse, are frequent during the treatment of hepatitis C infection.

Introduction

The World Health Organization estimates that more than 400 million people are infected with either hepatitis B virus (HBV) or hepatitis C virus (HCV), whereas approximately 150 million have chronic hepatitis C. Furthermore, hepatitis accounts for 80% of deaths by hepatic cancer [1].

Viral hepatitis, specifically hepatitis B and hepatitis C, not only cause liver disease but also can present with extrahepatic manifestations, including cutaneous lesions. Among all extrahepatic manifestations of liver diseases, cutaneous manifestations are the most common. In addition, they are easily recognizable and may provide the first clues of liver disease. The spectrum of cutaneous manifestations may vary during the acute and chronic phases of viral hepatitis [2, 3].

Hepatitis B

Epidemiology

HBV is an enveloped DNA virus and a member of the Hepadnaviridae family; it affects the liver, causing inflammation and hepatocellular necrosis. It is estimated that 240 million people are chronically infected worldwide. The main complications of chronic hepatitis B are cirrhosis and hepatocellular carcinoma. About 20–30% of individuals who become chronically infected

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will develop these complications, and an estimated 650,000 people each year die of chronic hepatitis B [4].

Low- prevalence areas of HBV carriers (0.1–2%) include Canada, the United States, western Europe, Australia, and New Zealand. High- prevalence areas worldwide (10–20%) include Southeast Asia, China, and sub-Saharan Africa. This wide variation of carriers can be explained by different transmission routes and the age at onset of infection. In low-prevalence areas the infection is acquired in adulthood by sexual or parenteral exposure. In high-prevalence settings the infection occurs by intrafamilial spread in the neonatal period or during childhood [5].

Clinical Presentation

The acute infection is symptomatic in only 30% of patients (icteric hepatitis), whereas the other 70% have subclinical or anicteric hepatitis. The incubation period lasts from 1 to 4 months and may be followed by serum sickness–like syndrome with jaundice, right upper quadrant pain, nausea, and anorexia [5].

Cutaneous manifestations of HBV infection are protean and nonspecific. Among patients with HBV infection, 20–30% develop the serum sickness–like disease, and 7–8% the polyarteritis nodosa (PAN) [3] (Box 40.1).

Therapeutic Approach

Antiviral therapies against HBV infection are available; they act to suppress viral replication, prevent the progression to cirrhosis, and reduce the risk of hepatocellular carcinoma and liver-related mortality. However, these treatments fail to eradicate the virus in most patients treated [4].

Seven antiviral agents are now approved for the treatment of chronic HBV infection: two formulations of interferon (IFN)-α (conventional and pegylated) and five nucleoside/nucleotide analogs (lamivudine, adefovir, entecavir, telbivudine, and tenofovir) [6].

Skin Manifestations of Hepatitis B Infection

The cutaneous manifestations of hepatitis B infection are summarized in Box 40.1.

Box 40.1 Skin Manifestations Related to Infection by Hepatitis B Virus

Serum sickness–like syndrome

Polyarteritis nodosa

Papular acrodermatitis of childhood

Serum Sickness-Like Syndrome

First described in 1843 by Graves, the serum sickness-like syndrome is currently considered the most common dermatologic manifestation associated with HBV [7, 8]. The syndrome occurs in the prodromal phase of infection by HBV, and it is estimated that 10–30% of the patients who have acute HBV will develop this transitory syndrome. It is also called "arthritis-dermatitis" and is clinically manifested by polyarthralgias or arthritis with joint swelling similar to that of acute rheumatoid arthritis [2, 7].

Arthritis can be either symmetric and generalized, involving the small joints of hands and feet, or asymmetric, involving the large and monoarticular joints. It is usually extremely painful, although joint injuries are not destructive and damage is not permanent [8].

Skin manifestations are varied. Rash is the most common and may be the only clinical manifestation of acute hepatitis [2]. The rash may be associated with hypocomplementemia; 4% of cases present with angioedema [2, 7].

Histopathology demonstrates leukocytoclastic vasculitis with endothelial edema, fibrinoid occlusion, and hemorrhage [7, 9]. Other skin lesions range from mild rashes to maculopapular, purpuric, or petechial exanthema. Lichenoid dermatitis and erythema multiforme may also occur [2]. In most cases, lesions follow or occur shortly after joint manifestations [8].

Pathogenesis includes the formation of circulating immune complexes including hepatitis B surface antigen (HBsAg), anti-HBs, immunoglobulins,

and complement, resulting in skin deposits and causing maculopapular lesions. Immune complexes cause lesions due to the production of C3a and C5 anaphylotoxins, manifested as rash and vasculitis [8].

Serum sickness-like syndrome may persist from days to months, and lasts for an average of 20 days [8].

Polyarteritis Nodosa

The association between HBV infection and PAN was first suggested in 1970 by Trepo and Thivolet [9]. PAN is considered one of the most severe syndromes associated with HBV. It is a rare complication of chronic HBV infection, occurring in approximately 1–5% of patients. However, HBsAg serum positivity is observed in 30–50% of PAN patients [2, 8]. The frequency of new cases of PAN related to HBV has decreased as a result of vaccination and improvements in the safety of blood products [8, 10].

Onset of symptoms, which include fever, malaise, arthralgias, abdominal pain, mononeuritis, polyarthritis, hypertension, and weight loss, occurs weeks to months after HBV infection. There may be progression of PAN with systemic involvement of other organs such as kidneys and gastrointestinal tract, as well as peripheral and central nervous systems. Hepatic manifestations vary from mild to moderate elevations of serum transaminases and cholestasis (rarely) [2]. According to the French Vasculitis Study Group, although the same clinical manifestations are present in patients with PAN related and not related to HBV, PAN patients are generally younger than 40 years and present with peripheral neuropathy (multiple mononeuritis), malignant hypertension, orchitis, cardiomyopathy, and intestinal ischemia [11].

Skin manifestations occur in 10–15% of cases and include palpable purpura in lower limbs that may progress to skin ulcers. Painful, purpuric subcutaneous nodules usually arise in the arterial path of lower limbs, as well as livedo reticularis. Rash and angioedema can also occur in patients with PAN associated with viral hepatitis B [7, 9].

Several hypotheses have been proposed to explain the pathogenesis of extrahepatic manifestations of HBV. The pathogenesis of HBV associated with PAN is a dynamic area of research in which the most current theories are associated with the deposit of immune complexes in the event of antigen excess. HBsAg (3 million kDa) and immune complexes are deposited in the lamina of affected arterioles. However, hepatitis B envelope antigen (HBeAg) (19 kDa) seems to play a predominant role in immune complexes due to its smaller size compared with HBsAg. Antineutrophil cytoplasmic antibodies (ANCA) are rarely identified in PAN related to HBV, unlike the cases of PAN not associated with this virus [2].

Histologically, vasculitis is characterized by fibrinoid necrosis and perivascular inflammation of small and medium-sized vessels. Afterward, mononuclear infiltrate predominates; vessel occlusion, thrombosis, ischemia, and necrosis may occur [8]. Immune responses associated with PAN usually begin within the first 6 months of viral hepatitis B infection [2]. Angiography findings include arterial microaneurysms, stenosis, and occlusion. In most PAN patients, renal angiography shows pathognomonic microaneurysms [8].

The prognosis of PAN related to HBV is bad if not treated, with a mortality rate of 30–50% in 5 years [2]. Conventional treatment of PAN not associated with HBV consists of corticosteroids, immunosuppressive drugs, and plasmapheresis. This treatment may have detrimental effects on PAN associated with HBV because of adverse effects on liver disease and viral replication [8]. The activity of PAN associated with HBV infection decreases after seroconversion for HBeAg and reduction of serum HBV levels. Thus, nucleotide analog antiviral therapy is necessary to treat this form of PAN. In cases of severe vasculitis, immunosuppression and removal of immune complexes with corticosteroids and plasmapheresis are used, followed by prolonged suppression (6–12 months) of HBV by using antiviral therapy [8, 10]. Recurrences are rare in PAN related to HBV, and do not occur when virus replication is terminated and seroconversion is achieved [12].

Papular Acrodermatitis of Childhood

Papular acrodermatitis of childhood (PAC) was first described in 1955 by Fernando Gianotti in Milan, Italy [13]. The following year, Gianotti

identified eight cases and published another article with Agostino Crosti [14]. After more than a decade, the relationship between viral infection and PAC was confirmed with the identification of a hepatitis B surface antigen (Australia antigen) in the blood of sick children [15]. In 1976, Ishimaru et al. described an epidemic of PAC associated with HBV in the city of Matsuyama, Japan, and proved the relationship between subtype ayw and HBsAg [16]. Other infectious agents are also related to PAC, including: Epstein–Barr virus, respiratory syncytial virus, cytomegalovirus, and enterovirus [9].

This syndrome affects children from 3 months to 15 years of age, with a peak between 1 and 6 years old. More than 90% of cases occur in children younger than 4 years. There is no predilection for race or gender, and seasonal variant reflects the natural history of the infectious agent. There is an increased incidence in children with personal or family history of atopy [17].

The pathogenesis is still unknown. Nowadays it is recognized that the development mechanism of lesions does not involve a direct local interaction between viral antigens and skin immune cells [17].

Clinically, PAC is manifested by a sudden onset of skin lesions, and in some cases there is prodromal pharyngitis, upper respiratory tract infection, or diarrhea. The most frequent lesions are multiple, pink to red-brown, slightly pruritic papules that may become confluent [7, 17]. Individual lesions present from 1 to 5 mm in diameter with occasional bleeding and, rarely, with scale [17]. Papules tend to be smaller (1–2 mm) the younger the child, with larger lesions (around 5 mm) occurring in older children (Fig. 40.1) [9]. The Koebner phenomenon may occur at an early stage [7]. Papules present symmetric distribution in the face, limbs, and gluteal area, sparing the trunk. They do not affect either the mucosa or the popliteal and cubital surfaces. Rash develops in about 2–3 days, but persists for 15–20 days [7, 9].

Hepatitis, generally anicteric, occurs within 7–14 days after the onset of skin lesions and reaches a peak when papules begin to disappear. The elevation of liver enzymes and hepatomegaly

Fig. 40.1 Papular acrodermatitis of childhood (Courtesy of Dermatology Department, Universidade Federal de Ciencias da Saude de Porto Alegre, Brazil)

persists for 2–3 months. Anti-HBs is not detected at the dermatitis stage, but has its peak incidence within 6–12 months later, suggesting that anti-HBs may play an important role in recovery. Inguinal and axillary lymphadenopathy is also common [7, 9].

The histopathology of skin lesions is characterized by perivascular lymphocytic infiltrate with mild endothelial edema [7].

Treatment usually is not necessary because the disease is self-limited and associated with few symptoms. The use of average-potency topical corticosteroids may shorten the duration of lesions. Pruritus, when present, may be treated with antihistamines [17].

Hepatitis C

Epidemiology

HCV is a single-stranded RNA virus of the Flaviviridae family, first detected in 1989. It comprises nearly 10,000 nucleotides whose sequence categorizes HCV into six main genotypes and several subtypes. It is currently the major cause of liver disease and significantly affects the health of a large number of people. Although the estimated number of infected individuals exceeds 170 million, the prevalence of infection varies in different geographic locations [18].

Individuals with exposure to blood or blood products present an increased risk of HCV infection. Intravenous drug users, transplant patients, and health professionals are included in this group. Both sexual and vertical transmission correspond to the minority of cases [9, 18].

Clinical Presentation

Acute hepatitis develops after 4–12 weeks of incubation and is asymptomatic in most cases. Only 25% of cases present symptoms, usually nonspecific, including: fatigue, weakness, anorexia, myalgia, and, rarely, jaundice. Progression to chronic disease occurs in 70–80% of infected patients. Cirrhosis occurs in approximately 20% of cases, and hepatocellular carcinoma in 16% [9, 18].

Extrahepatic manifestations of HCV infection were first described in 1990 and can affect several organs. Forty percent to 75% of patients with chronic HCV infection present at least one extrahepatic manifestation [19].

Approximately 17% of HCV-infected patients have at least one skin manifestation, which may be induced directly or indirectly by HCV. Skin diseases certainly related with chronic HCV infection include cryoglobulinemia, lichen planus (LP), and porphyria cutanea tarda (PCT). In these diseases it is recommended to carry out the testing for HCV infection. Psoriasis, chronic pruritus, and necrolytic acral erythema present possible association with HCV infection. Anecdotal cases are described in patients with chronic rash and vitiligo (Box 40.2) [20].

Therapeutic Approach

Until a few years ago, standard HCV treatment was based on the use of pegylated IFN-α and ribavirin. In 2011, two protease inhibitors, telaprevir and boceprevir, were approved for treatment of patients with genotype 1, to be used in triple combination with IFN and ribavirin. Since 2014, several direct-acting antivirals have been approved, allowing patients to be treated without IFN with high rates of sustained virologic response [21].

Skin Manifestations of Hepatitis C Virus Infection

The cutaneous manifestations of HCV are summarized in Box 40.2.

> **Box 40.2 Skin Diseases and Infection with Hepatitis C**
>
> *Proven association*
> Mixed cryoglobulinemia
> Porphyria cutanea tarda
> Lichen planus
> *Possibly related*
> Psoriasis
> Chronic itching
> Necrolytic acral erythema

Mixed Cryoglobulinemia

Cryoglobulins are anti-immunoglobulins precipitated at low temperatures, and the type of cryoglobulin is used to classify cryoglobulinemia types I, II, and III [9, 18].

Type I is characterized by monoclonal immunoglobulin (Ig), usually IgG or IgM, associated with Waldenstrom macroglobulinemia, multiple myeloma, and chronic lymphocytic leukemia. In cryoglobulinemia type II, there is presence of monoclonal IgM (rheumatoid factor) and polyclonal IgG. Type III is characterized by IgG and polyclonal IgM [2].

The type of cryoglobulinemia most commonly related to HCV is type II. These immunoglobulins may reversibly precipitate at temperatures below 37 °C and form immune complexes with complement, viral antigens and HCV RNA in small and medium-sized blood vessels (arterioles, capillaries, and venules) [2].

Despite the high prevalence of HCV markers in patients with mixed cryoglobulinemia, only 13–54% of patients with chronic HCV infection will develop cryoglobulinemia [9].

The target organs are skin, joints, nervous system, and kidney. Expression of the disease varies from mild symptoms to a life-threatening clinical presentation [22].

The skin is the organ most frequently involved and the most common sign is palpable purpura,
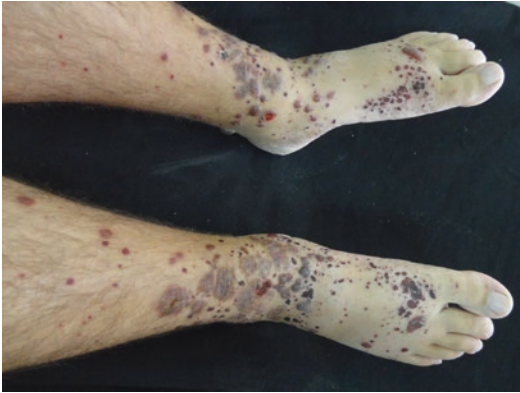
which occurs in 70–90% of patients [22]. It begins in the lower limbs and can extend up to the abdominal region, trunk, and upper limbs (Fig. 40.2). Lesions persist for 3–10 days, with late residual brownish pigmentation. Histologically there is unspecific leukocytoclastic vasculitis involving the small vessels with inflammatory infiltrate, and in some cases fibrinoid necrosis and endovascular thrombus. Other manifestations include urticarial vasculitis, livedo, rash, Raynaud's phenomenon, and leg ulcers [22, 23].

The most common symptoms are fatigue, which occurs in 80–90% of patients. Bilateral and symmetric arthralgia are observed in 40–60% of cases and involve, primarily, knees and hands and rarely, elbows and ankles. Arthritis occurs in less than 10% of cases. Neurologic manifestations range from sensory axonopathy to multiple mononeuropathy. The most common form is distal sensory or sensorimotor polyneuropathy. Motor deficit is uncommon and affects mainly the lower limbs, appearing months to years after sensory symptoms [23].

Involvement of the central nervous system (<10% of patients) is characterized by stroke, epilepsy, or cognitive impairment. Kidney changes are reported by 20–35% of patients. The most frequent clinical and pathologic presentation is acute or chronic membranoproliferative glomerulonephritis type I with endothelial deposit. The most common clinical presentation is proteinuria with microscopic hematuria and variable stages of kidney failure. Other manifestations include xerophthalmia, xerostomia, abdominal pain, and heart and lung involvement [23].

In general, HCV-positive patients have more cutaneous involvement than neurologic involvement [18].

Laboratory findings include a slight increase in transaminases and the presence of rheumatoid factor in 70% of patients [18].

Cryoglobulinemia survival rates at 1, 3, 5, and 10 years are, respectively, 96%, 86%, 75%, and 63% in HCV-positive patients. Mortality is caused by severe infection and advanced liver disease. Factors related to worst prognosis are the presence of severe hepatic fibrosis, and involvement of the central nervous system, kidney, and heart [24].

The therapy for cryoglobulinemia associated with HCV includes elimination of virus, reduced lymphocyte proliferation, and management of cutaneous vasculitis [2]. In mild to moderate disease, pegylated IFN and ribavirin (and protease inhibitor of HCV genotype 1) are the initial choice. In severe cases, a combination of rituximab and pegylated IFN/ribavirin targets the virus and cryoglobulin-producing cells [2, 18].

Porphyria Cutanea Tarda

PCT is characterized by abnormal porphyrin metabolism secondary to a decreased activity of the hepatic enzyme uroporphyrinogen decarboxylase (URO-D) [9].

The familial form is inherited as an autosomal dominant trait and is associated with 50% reduction of URO-D activity throughout the body. The sporadic form is responsible for most cases of PCT and occurs in predisposed individuals. In these individuals, only hepatocytes show a reduction in the activity of URO-D. Alcohol, estrogens, hexachlorobenzene, iron accumulation, and exposure to HCV are extrinsic factors that act as triggers to the appearance of PCT in predisposed individuals [9, 18].

Epidemiologic association between PCT and HCV infection is strong, with rates of 70–90% in southern Europe and 20% in northern Europe, Australia, and England. According to studies, when adjusted for variation and geographic variability,

the association between PCT and HCV remains significant, with an average prevalence rate of 50% of HCV in patients with PCT [18, 20].

HCV increases the production of reactive oxygen species, leading to downregulation of liver hepcidin, a key regulator of absorption and metabolism of iron. This contributes to iron overload in addition to other factors, such as genetic predisposition. Thus, there is decreased activity of URO-D [20].

Cutaneous manifestations include vesicles, blisters, erosions, and crusting that usually occur days after exposure to sunlight or trauma. They may result in scarring, miliary cysts, and hyper-/hypopigmentation (Figs. 40.3 and 40.4). Photosensitivity, skin fragility, facial hypertrichosis and sclerodermi-

Fig. 40.3 Porphyria cutanea tarda (Courtesy of Dermatology Department, Universidade Federal de Ciencias da Saude de Porto Alegre, Brazil)

Fig. 40.4 Porphyria cutanea tarda: blisters and vesicles (Courtesy of Dermatology Department, Universidade Federal de Ciencias da Saude de Porto Alegre, Brazil)

form plaques may also occur. There is no difference in skin manifestations of PCT between HCV-positive and HCV-negative patients [2, 20].

Increased urocarboxyl porphyrins and heptacarboxyporphyrin in urine, and the presence of isocoproporphyrin in feces, are typical laboratory findings. Increases in liver enzymes, ferritin, and serum iron also occur [18].

Antiviral treatment may improve the clinical manifestations and laboratory findings, especially when preceded by therapeutic phlebotomy. Since iron is also involved in the progression of liver disease associated with HCV, reduction of iron stores due to phlebotomy can improve both conditions [20].

Lichen Planus

LP is a chronic inflammatory disease that can affect the skin, scalp, nails, and mucosa. The exact prevalence is unknown, but it is estimated to affect 0.9–1.2% of the general population [25]. The disease is slightly more common in women than in men and occurs at any age, but is more frequent in the fifth decade of life [9].

Several studies confirm that HCV is the main LP-related liver disease [25]. In 1991, Mokni et al. described the first case of LP confirmed by biopsy in a patient with active chronic hepatitis induced by HCV [26]. Since then, the association between LP and chronic HCV infection has been reported in several epidemiologic studies, with contradictory results depending on the design and specific prevalence in each country [9, 20]. In hyperendemic areas such as Egypt, Japan, and southern Europe, the association rate is around 35%, while in northern European countries that have low incidence rate it is 0.5% [20]. Two meta-analysis studies support the association between chronic HCV infection and LP. LP patients have a fivefold higher-risk of HCV infection when compared with controls [27]. The odds ratio for the diagnosis of LP in HCV patients is 2.5. HCV-related oral LP is associated with the HLA-DR6 allele, and the idiopathic forms of LP with the HLA-DR1 allele [25].

Clinically it is characterized by small, planar, polygonal, purple, and pruritic papules. LP affects the extremities (flexor surfaces of the wrists,

forearms, and legs) and mucosa. Skin lesions are typically bilateral and symmetric, covered by white, reticulated lines, called Wickham's striae (Fig. 40.5). LP lesions related to HCV are similar to those described in classic LP patients [9, 25].

LP involving mucosa is more frequent in the oral cavity, but can also involve the genital area. Oral LP may be reticular, erosive, atrophic, papular, plaque-like, or bullous (Fig. 40.6) [25]. Oral LP is the clinical phenotype most studied in patients with chronic HCV infection, and the most severe and recurrent clinical variant is the erosive form [20]. Between 1% and 6% of patients with chronic HCV infection have evidence of oral LP, while the prevalence of HCV infection in patients with oral LP is approximately 27% [2].
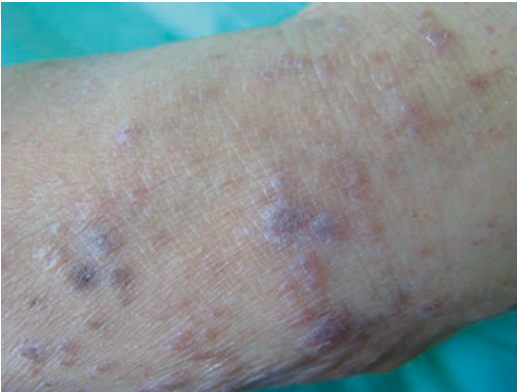
Fig. 40.5 Lichen planus (Courtesy of Dermatology Department, Universidade Federal de Ciencias da Saude de Porto Alegre, Brazil)

Fig. 40.6 Oral lichen planus (Courtesy of Dermatology Department, Universidade Federal de Ciencias da Saude de Porto Alegre, Brazil)

Histologically, there is lymphocytic infiltrate in the subepidermal band associated with the destruction of keratinocytes in the basal layer, sawtooth epidermal ridges, and pigmentary incontinence [9].

Although the association between LP and HCV is well documented, the pathogenesis remains uncertain. A current hypothesis relates LP to an autoimmune response, mediated by T cells, to a viral protein or a self epitope shared by the virus and present in basal keratinocytes, which are attacked by cytotoxic CD8 T cells [20].

Management of cutaneous LP is similar in HCV-positive and -negative patients. The first-line therapy is topical corticosteroids. In patients with extensive skin lesions, systemic corticosteroids and phototherapy may be used [9]. Contrary to cutaneous LP, oral LP tends to be chronic, with periods of remission and exacerbation. Studies of the use of IFN and ribavirin have shown as much benefit as exacerbation of oral LP in HCV-positive patients. With the direct-action antiviral agents currently available for the treatment of HCV infection, the exacerbation of LP with antiviral therapy is less worrisome. In oral LP the first-line treatment is topical corticosteroids, with a choice of topical calcineurin inhibitors in refractory cases. In cases that do not respond to these treatments, oral corticosteroids and immunomodulators can be used [2].

Skin Diseases with Possible Association with HCV

Psoriasis

Chronic HCV infection and other liver diseases represent some of the many comorbidities that affect patients with psoriasis. The epidemiologic association between psoriasis and chronic HCV infection has been described mainly by clinical studies of population-based hospitals and observational studies in countries with a heterogeneous burden of HCV and psoriasis [20].

Increased risk of HCV infection among patients with mild to moderate psoriasis and psoriatic arthritis was reported in Taiwan, Japan, and Italy, regardless of exposure to antiviral treatment with IFN [20].

Another observational study in the United States did not confirm these findings, probably because of different methodology and the small sample of patients with psoriasis [28]. However, a case–control study of a large number of psoriasis patients by Cohen et al. in 2010 supports previous reports of an association between psoriasis and hepatitis C [29].

A recent study in Japan showed that patients with psoriasis associated with HCV have the following profile: male dominance, relatively late onset of psoriasis, a mean age of 54 years, HCV infection prior to psoriasis in most cases, and association with diabetes mellitus in 35% of patients [30]. In Egypt, one of the areas with the highest prevalence of HCV infection in the world, a study of 100 patients with psoriasis showed a prevalence of 19% of HCV infection while HIV-positive psoriatic patients had more severe psoriasis, needing systemic treatment of longer duration [31]. An abnormal expression of apoptosis regulatory proteins in addition to the HCV infection seems to be related to the severity of psoriasis in these individuals [32].

This evidence supports the role of HCV infection as a trigger for psoriasis in genetically predisposed individuals [20, 31].

Chronic Itching (Pruritus)

Itching is a common symptom in liver diseases, mainly in chronic cholestatic diseases such as primary biliary cirrhosis and primary sclerosing cholangitis [20].

This symptom occurs in about 2.5–23% of chronic HCV patients. The cause is not fully understood, although it may be associated with liver fibrosis, bile duct lesions, and cholestasis [33]. Autotaxin and its product, lysophosphatidic acid, have recently been found in the pathophysiology of itch, as well as in cholestatic liver disease. In chronic HCV infection, autotoxin and lysophosphatidic acid activities are increased, showing a solid correlation with the stage of liver cirrhosis, and its complications and prognosis [20].

In an early infection, itching may be acute and transitory, or persistent in chronic HCV infection. Clinically it may present in two forms: generalized itch in normal skin or itching associated with secondary lesions (papules, nodules, excoriations, or lichenification) [20].

Necrolytic Acral Erythema

Necrolytic acral erythema (NAE) belongs to the family of migratory erythemas, which includes necrolytic migratory erythema, enteropathic acrodermatitis, and other dermatosis secondary to nutritional deficiencies. Clinically and histologically these entities are similar, but present diverse etiology [34, 35].

This dermatosis was first described in 1996, in a cohort involving seven HCV-infected patients from Egypt [35].

NAE symptoms include itching (93% of cases), burning (16% of cases) and/or pain (14% of cases). Erythematous papules, blisters, or erosive lesions are seen at the acute stage. Chronic lesions are characterized by well-defined hyperkeratotic plaques, circled by erythema or hyperpigmentation. In most cases, lesion distribution includes the backs of feet and hands. They occasionally occur in other locations such as legs, knees, and elbows [36].

Physiopathologic mechanisms are not fully understood. The cause of NAE may be multifactorial, whereby liver dysfunction plays a role in the development of cutaneous disease [36]. In some cases, disease remission occurs after oral administration of zinc, although the exact mechanism of this therapeutic response remains unknown [37].

In histopathology, psoriatic epidermal hyperplasia with a variety of other findings has been identified, including dermal inflammation and necrosis of epidermal cells [38].

NAE differs from other necrolytic erythemas because of an acral distribution of lesions and the universal association with HCV infection. It is important to recognize this association because cutaneous manifestations of NAE precede the diagnosis of HCV infection [35].

Adverse Cutaneous Reactions Related to HCV Treatment

HCV treatment with IFN and ribavirin may cause either adverse cutaneous reactions at the site of application or diffuse cutaneous reactions (Box 40.3) [18, 39].

Local cutaneous reactions occur in 12–20% of patients and include erythema, abscess, vesicular-bullous reactions, ulcer, and necrosis [18].

Nearly 25% of patients in treatment with IFN and ribavirin present diffuse cutaneous reactions [18, 39]. Pruriginous cutaneous eruption is the most frequent, occurring in 8–10% of patients. It is characterized by itching, xerosis, and erythematous papules on the trunk and extremities [39, 40]. Transitory alopecia and effluvium have also been described [18, 39].

Two protease inhibitors, boceprevir and telaprevir, have been available since 2011 for the treatment of chronic infection with type 1 HCV genotype, in combination with IFN and ribavirin [40]. This triple therapy increases sustained viral response up to 70%, depending on the characteristics of the virus and the host [41]. During the triple therapy, cutaneous reactions are, in most cases, mild (37%) to moderate (14%) [40, 42]. Lesion patterns are similar to the eruption associated with IFN and ribavirin with no protease inhibitor, but with an increase of frequency (55% versus 33%) and severity (3.7% versus 0.9%). Only 6% of patients in triple therapy present severe cutaneous reactions, and few develop Stevens–Johnson syndrome or DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) [40].

Box 40.3 Adverse Cutaneous Reactions Related to HCV Treatment

Local	Diffuse
Erythema	Maculopapular exanthema
Abscess	Itching (pruritus)
Vesicular-bullous reactions	Rash
Ulcer and necrosis	Photosensitivity
	Alopecia

Glossary

Cryoglobulinemia Characterized by the presence of cryoglobulins in the serum. This may result in a clinical syndrome of systemic inflammation caused by cryoglobulin-containing immune complexes.

Jaundice Yellowish discoloration of the skin, white of the eyes, and mucous membranes caused by deposition of bile salts in the tissues.

Hepatitis Inflammation of the liver, caused by a virus or a toxin and characterized by jaundice, liver enlargement, and fever.

Polyarteritis nodosa Systemic necrotizing vasculitis that predominantly affects medium-sized muscular arteries and often involves small muscular arteries, resulting in secondary tissue ischemia.

Porphyria Group of diseases in which there is abnormal metabolism of the blood pigment hemoglobin.

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Skin Manifestations with HIV/AIDS

41

Márcia S. Zampese, Gabriela Czarnobay Garbin, and Bruna Guerra Rech

Key Points

- Cutaneous disorders develop in over 90% of HIV-infected persons at some time during the course of the illness; they have been a basic index for the presence and course of HIV infection as well as a challenging task for health care providers because of the severe and recalcitrant nature of such conditions
- Mucocutaneous disease has changed its spectrum after the antiretroviral therapy (ART) introduction. In the pre-ART era major presentations were the opportunistic infections-related skin diseases, whereas the noninfectious skin diseases emerged in the current ART era
- The use of ART in HIV-infected patients results in the immunologic system recovery that can trigger immunopathologic lesions as well as systemic inflammatory reactions, the so-called immune reconstitution inflammatory syndrome

"Ce qu'il y a de plus profond dans l'homme, c'est sa peau.
La peau humaine separe le monde en deux espaces. Cote couleurs, cote douleurs."

Paul Valery

"In the face of AIDS, we must deepen and broaden the philosophy and the practice of health promotion, for it will lead us to the very frontiers of our knowledge of others, and ourselves."

Jonathan Mann

Introduction

In 1981, a new outbreak of opportunistic infections (OIs) and Kaposi's sarcoma was reported among homosexual men in the United States [37, 38]. Thanks to the massive damage to the immune system, this fatal disease was named the acquired immunodeficiency syndrome (AIDS). Shortly after, the syndrome was also reported in hemophiliacs, blood transfusion recipients, injection drugs users, and newborn children of affected mothers [243]. Soon an epidemic of AIDS was noticed among heterosexuals in Africa, mainly

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affecting women [242]. The retrovirus later named human immunodeficiency virus (HIV) was identified in 1983 as the causal agent of AIDS [95]. Two types of HIV are known: HIV-1 is the most common and is found worldwide; HIV-2 is a less virulent variant distributed in West and Central Africa [30].

Both HIV diagnosis and treatment have significantly evolved since the initial recognition of AIDS, and the use of antiretroviral therapy (ART) has led to a dramatic reduction in HIV-associated morbidity and mortality [243]. ART has also modified the patterns of HIV-associated cutaneous manifestations. The variability of these skin and mucosal lesions is related to a multitude of clinical situations: HIV-infected patients without AIDS, patients with advanced AIDS, patients with diffuse inflammatory reaction generated by the effectiveness of ART (known as immune reconstitution inflammatory syndrome (IRIS)), and also adverse effects of ART itself. A complex scenario arises from the interaction between HIV and infected host, and dermatologic disorders can be present at any point of the spectrum of HIV disease. The skin and mucosa can be sensitive indicators of underlying immunosuppression, and mucocutaneous disorders are often the first manifestation of HIV infection and advancing immunodeficiency. Both the World Health Organization (WHO)

clinical staging of HIV/AIDS and the Centers for Disease Control and Prevention (CDC) classification system for HIV infection and AIDS case definition (for adults and adolescents) include 19 and 16 disorders, respectively, that may potentially affect the skin and mucosa [39, 318] (Boxes 41.1 and 41.2). Cutaneous disorders develop in more than 90% of HIV-infected persons at some time during the course of the illness; they have been a basic index for the presence and course of HIV infection, and can be a challenging task because of the severe and recalcitrant nature of such conditions [42, 56, 303, 321]. Since the early description of AIDS over three decades ago, dermatologists have continued to play an important role in recognizing cutaneous markers of HIV infection, treating mucous and skin disorders associated with HIV, and helping to curb the spread of HIV by control of other sexually transmitted infections [303]. The aim of this chapter is to enhance awareness and familiarize healthcare providers with the most frequent cutaneous manifestations associated with HIV and AIDS so that they can recognize the possibility of an underling HIV infection, recommend appropriate testing, and provide timely and suitable management for either disease. We discuss the most frequent mucous and skin disorders associated with HIV/AIDS, which are listed in Table 41.1.

Table 41.1 Skin manifestations and disorders in HIV-infected individuals

Infectious skin disorders	Infectious skin disorders	Noninfectious skin disorders
Viral	*Fungal*	*Xerosis*
Acute HIV infection	Candidiasis	*Seborrheic dermatitis*
Herpes simplex	Dermatophytosis	*Psoriasis*
Varicella zoster virus	Cryptococcosis	*Papular pruritic dermatoses*
Molluscum contagiosum	Histoplasmosis	Eosinophilic folliculitis
Oral hairy leukoplakia	Sporotrichosis	Papular pruritic eruption
Human papillomavirus	*Ectoparasitic infestations*	*Antiretroviral therapy–associated manifestations*
Acquired epidermodysplasia verruciformis	Scabies	Adverse drug reactions
	Demodicidosis	Immune reconstitution inflammatory syndrome
Bacterial	*Protozoal diseases*	*Neoplastic disorder*
Cutaneous bacterial infections	Tegumentary leishmaniasis	Kaposi's sarcoma
Syphilis		
Bacillary angiomatosis		
Mycobacterial infections		

Box 41.1 1993 CDC Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults

CD4+ T-Lymphocyte Categories

Category 1: ≥500 cells/mL

Category 2: 200–499 cells/μL

Category 3: <200 cells/μL

Clinical Categories

Category A

Asymptomatic HIV infection

Persistent generalized lymphadenopathy

Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

Category B

Bacillary angiomatosis

Candidosis, oropharyngeal (thrush)

Candidosis, vulvovaginal; persistent, frequent, or poorly responsive to therapy

Cervical dysplasia (moderate or severe)/cervical carcinoma in situ

Constitutional symptoms, such as fever (38.5 °C) or diarrhea lasting >1 month

Hairy leukoplakia, oral

Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome

Idiopathic thrombocytopenic purpura

Listeriosis

Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess

Peripheral neuropathy

Category C

Candidosis of bronchi, trachea, or lungs

Candidosis, esophageal

Cervical cancer, invasive[a]

Coccidiomycosis, disseminated or extrapulmonary

Cryptococcosis, extrapulmonary

Cryptosporidiosis, chronic intestinal (>1 month duration)

Cytomegalovirus disease (other than liver, spleen, or nodes)

Cytomegalovirus retinitis (with loss of vision)

Encephalopathy, HIV-related

Herpes simplex: chronic ulcer(s) (>1 month duration); or bronchitis, pneumonitis, or esophagitis

Histoplasmosis, disseminated or extrapulmonary

Isosporiasis, chronic intestinal (> 1 month duration)

Kaposi's sarcoma

Lymphoma, Burkitt's (or equivalent term)

Lymphoma, immunoblastic (or equivalent term)

Lymphoma, primary, of brain

Mycobacterium avium complex or *M. kansasii*, disseminated or extrapulmonary

Mycobacterium tuberculosis, any site (pulmonary[a] or extrapulmonary)

Mycobacterium, other species or unidentified species, disseminated or extrapulmonary

Pneumocystis carinii pneumonia

Pneumonia, recurrent[a]

Progressive multifocal leukoencephalopathy

Salmonella septicemia, recurrent

Toxoplasmosis of brain

Wasting syndrome due to HIV

CDC [39]

[a]Added in the 1993 expansion of the AIDS surveillance case definition

Box 41.2 WHO Clinical Staging of HIV/AIDS for Adults and Adolescents with Confirmed HIV Infection

Clinical stage 1 (asymptomatic)

Asymptomatic

Persistent generalized lymphadenopathy

Clinical stage 2 (mild symptoms)

Moderate unexplained weight loss (<10% of presumed or measured body weight)I

Recurrent respiratory tract infections sinusitis, tonsillitis, otitis media, and pharyngitis)

Herpes zoster

Angular cheilitis

Recurrent oral ulceration

Papular pruritic eruptions

Seborrheic dermatitis

Fungal nail infections

Clinical stage 3 (advanced symptoms)

Unexplained[a] severe weight loss (>10% of presumed or measured body weight)

Unexplained chronic diarrhea for longer than 1 month

Unexplained persistent fever (above 37.6 °C intermittent or constant, for longer than 1 month)

Persistent oral candidiasis

Oral hairy leukoplakia

Pulmonary tuberculosis (current)

Box 41.2 (continued)

Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, or bacteremia)

Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis

Unexplained anemia (<8 g/dL), neutropenia (<0.5 × 10⁹ per liter) or chronic thrombocytopenia (<50 × 10⁹ per liter)

Clinical stage 4[b] (severe symptoms)

HIV wasting syndrome

Pneumocystis pneumonia

Recurrent severe bacterial pneumonia

Chronic herpes simplex infection (orolabial, genital, or anorectal of >1 month duration or visceral at any site)

Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)

Extrapulmonary tuberculosis

Kaposi's sarcoma

Cytomegalovirus infection (retinitis or infection of other organs)

Central nervous system toxoplasmosis

HIV encephalopathy

Extrapulmonary cryptococcosis including meningitis

Disseminated nontuberculous mycobacterial infection

Progressive multifocal leukoencephalopathy

Chronic cryptosporidiosis (with diarrhea)

Chronic isosporiasis

Disseminated mycosis (coccidiomycosis or histoplasmosis)

Recurrent nontyphoidal *Salmonella* bacteremia

Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumors

Invasive cervical carcinoma

Atypical disseminated leishmaniasis

Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

WHO [318]

Assessment of body weight in pregnant woman needs to consider the expected weight gain of pregnancy

[a]Unexplained refers to where the condition is not explained by other causes

[b]Some additional specific conditions can also be included in regional classifications (such as reactivation of American trypanosomiasis [meningoencephalitis and/or myocarditis]) in the WHO Region of the Americas and disseminated penicilliosis in Asia)

Infectious Skin Disorders

Viral Diseases

Acute HIV Infection

Acute HIV infection is also known as primary HIV infection or acute retroviral syndrome. Primary HIV infection refers to the earliest stages of infection, or the interval from initial infection to seroconversion. During this stage, many patients have symptoms of acute HIV-1 illness; they also have very high HIV RNA levels and negative or indeterminate findings in HIV-1 antibody tests.

Etiopathogenesis and General Epidemiology

As with other severe viral infections, HIV-1 infection is associated with an array of clinical manifestations, known as acute retroviral syndrome (ARS), which usually occurs between the first and third week after infectious exposure. ARS is the early manifestation of HIV-1 infection and is associated with high levels of viral replication. The presentation is unspecific, and a mononucleosis-like acute disease occurs in up to 93% of patients [165].

Clinical Presentation

The main clinical findings of ARS include fever, pharyngitis, lymphadenopathy, fatigue, weight loss, and myalgia [55]. The general symptoms may be followed by a transitory morbilliform exanthema or erythematous-scaling papules on the trunk, head, and neck, with centrifugal progression. Oral candidiasis and painful oral and genital ulcers may also develop. Headache, meningismus, and ocular pain are the most frequent neurologic manifestations [31, 165]. Box 41.3 summarizes the most common symptoms associated with ARS. In the prospective study by Braun and colleagues [31], almost one-third of the patients had atypical ARS, from asymptomatic ARS to patients with a wide spectrum of symptoms, usually gastrointestinal and neurologic symptoms. ARS is self-limited, and most of the signs and symptoms disappear in 3–4 weeks. Nevertheless, some patients may present symptoms up to 3 months after exposure [305].

Complementary Examinations

Following HIV infection, serologic markers of the infection appear in a chronologic sequence: viral RNA, p24 antigen, and anti-HIV antibody (Fig. 41.1). About 2 weeks after infection, viremia increases, and then declines to a steady-state level as the humoral and cell-mediated immune responses control HIV replication. This time interval, the serologic "window period," is characterized by seronegative tests, occasionally detectable antigenemia, viremia (as measured by RNA), and variable CD4 lymphocyte levels [54, 59]. Diagnostic tests for primary HIV-1 infection include assays for HIV-1 RNA, p24 antigen, and enzyme immunoassay antibody tests (Table 41.2). Upon encountering high-risk patients with clinical suspicion and a negative or indeterminate HIV-1 antibody test result, confirmation of acute infection requires detection of HIV-1 RNA or p24 antigen, but tests designed for this purpose are not routinely available. A fourth-generation enzyme-linked immunosorbent assay (ELISA) that can concomitantly detect viral p24 antigen and antiviral antibodies is an alternative and more practical strategy [55, 65].

Therapeutic Approach

Given the potential benefits for public and individual health, some treatment guidelines have recommended early ART for patients with acute HIV infection [55, 108, 147]. The introduction of ART before HIV seroconversion decreases the size of the latent viral reservoir, reduces immune activation, and possibly protects against the infection of central memory T cells. Benefits peak during the first weeks after HIV infection, although they are noticeable up to the first 6 months. However, early treatment does not prevent the establishment of the HIV latent reservoir [49, 275].

Herpes Simplex Virus

Human herpes simplex viruses (HSVs) are ubiquitous pathogens with a large reservoir in the general population. HSV-associated diseases are among the most widespread infections; they are incurable and persist in latent form during the host's lifetime. There are two HSV types, HSV
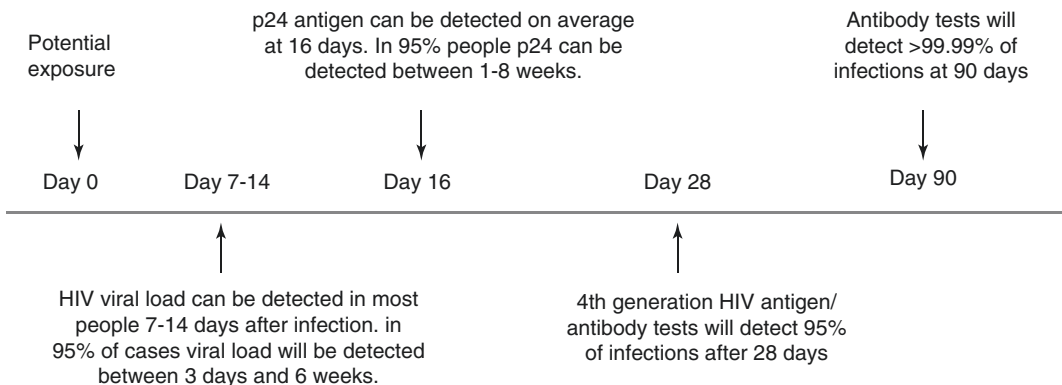
Fig. 41.1 Timeline of HIV serologic markers after exposure

Table 41.2 Tests for HIV-1

Test	Detection		
	RNA/DNA	Antigen	Antibody
PCR/viral load	X	–	–
p24 antigen test	–	X	–
4th generation Ag/Ab tests (p24+ ELISA, ELI, MEIA/ELFA/ECLIA)	–	X	X
1st/2nd/3rd generation Ab only tests (ELISA, ELI, MEIA/ELFA/ECLIA	–	–	X
Rapid tests: finger prick or oral swab	–	–	X
Western blot tests (confirmatory)	–	–	X

Cohen [54, 55], and Constantine [59]
Ab antibody, *Ag* antigen, *PCR* polymerase chain reaction

type 1 (HSV-1) and HSV type 2 (HSV-2), which are closely related but differ in epidemiology [81, 158]. HSV-1 is usually associated with orofacial disease, whereas HSV-2 is related with genital disease; however, lesion location is not necessarily indicative of viral type.

General Epidemiology

Globally, an estimated two-thirds of the population under 50 years old is infected with HSV-1 and 16% with HSV-2, according to WHO global estimates [161, 162]. Taken together, estimates reveal that over half a billion people between the ages of 15 and 49 years have genital infection caused by either HSV-1 or HSV-2 [161, 162]. Genital herpes may be caused by either HSV-1 or HSV-2 but, globally, the large majority of cases are caused by HSV-2; infection is common in both the industrialized and developing worlds, and HSV-2 uncommonly causes infection by nonsexual means [161, 162]. HSV-2 prevalence varies according to the geographic site, age, sex, investigated population, and HIV-1 status [47]. More women than men are infected with HSV-2, and prevalence increases with age, most markedly in the younger ages, slightly declining after 40 years of age [161,

162]. Despite the majority of genital herpes cases resulting from HSV-2, a growing proportion of the anogenital herpes infections has been attributed to HSV-1, particularly among young women and men who have sexual intercourse with other men (MSM) [40]. HSV infection is frequent among HIV-infected patients, with an estimated prevalence of 27%, when the CD4 count is <100 cells/mm^3 [140]; additionally, atypical clinical presentations are more frequent, and a possible spontaneous resolution occurs on a small scale when compared with noninfected HIV patients [199].

Etiopathogenesis

Herpes simplex is an infection resulting from HSV-1 and HSV-2, which are enveloped α-herpesviruses with double-stranded DNA. Both HSV types are distinguished by antigenic differences in their enveloping proteins [21, 199]. HSV infection accounts for a recurrent disease that persists over life, with no cure. Transmission occurs via direct contact with infectious secretions on the mucosae or wounded skin. Most infections are transmitted via asymptomatic viral shedding [21]. The natural history includes first-episode mucocutaneous infection, establishment of latency, and subsequent reactivation. The primary infection via HSV is followed by intense viral replication at the inoculation site. Early infection at the oral cavity results in HSV latency in the trigeminal ganglion, whereas in the genital primary infection the viral latency is located in the sacral ganglion [198].

Inter-relationship Between HSV and HIV

HSV-2 and HIV-1 infections facilitate each other's acquisition, transmission, and disease progression [300]. Epidemiologic data show a relationship between HSV-2 and HIV-1 prevalence. HSV-2 seroprevalence varies from 22% in sexually active adults in the United States to 60% in HIV-1 negative women in the sub-Saharan Africa, and to even more than 80% among HIV-1 infected individuals [151, 313]. The biological background for how HSV-2 increases a host's susceptibility to HIV-1 rests on several interact-
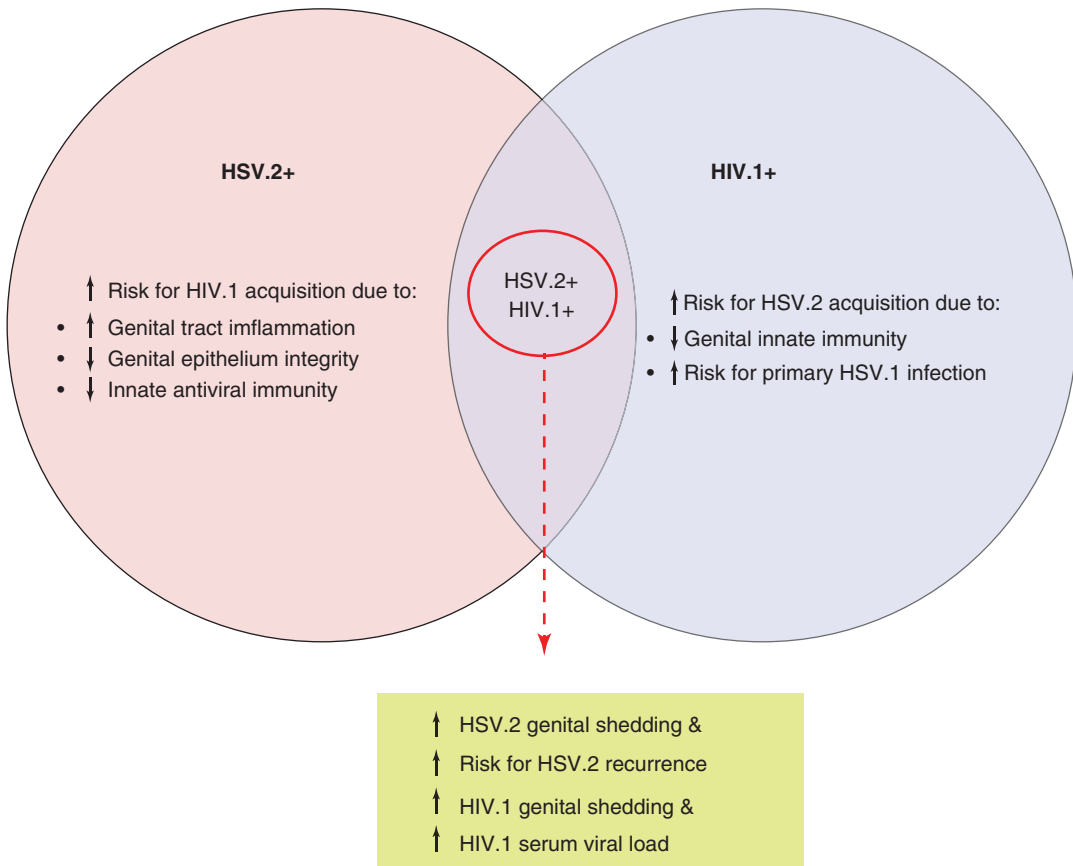
Fig. 41.2 Inter-relationships between HSV and HIV [300]

ing mechanisms: HSV-2 infection increases the concentration of cervical HIV-1 target cells, decreases mucosal innate immunity, and induces a mucosal inflammatory response [300]. The synergistic relationship between HIV-1 and HSV-2 is depicted in Fig. 41.2. HSV-2 infection seems to increase the woman's susceptibility to HIV-1 infection the same way as the opposing situation, that is, HIV-1 positive women display deficient mucosa immunity against the HSV-2 primary infection or reactivation [252]. The HIV-1 and HSV-2 viruses seem to have a synergistic relationship that favors the host's viral shedding: HIV-1-infected women shed more HSV-2 virus, and HSV-2 suppression also seems to decrease HIV-1 viral load in serum as well as HIV-1 shedding in the genital tract [160, 252].

Clinical Presentation

HIV patients with a CD4 count >100 cells/mm^3 show a clinical presentation similar to that of an immunocompetent patient: painful vesicles are grouped under the erythematous base that erupt and make polycyclic lesions with an erythematous halo, usually located in the mouth (Fig. 41.3), genitals (Fig. 41.4), perianal region, and distal parts of fingers. In patients with advanced immunosuppression, the lesions are larger and/or multiple (Fig. 41.5), possibly coalescing and evolving into deep ulcers (Fig. 41.6), with more severe and frequent recurrences; chronic skin lesions may develop an atypical verrucous appearance [140, 141, 209]. Local prodromal symptoms (burning, pruritus, tingling) may occur in recurrences, hours or days before development of lesions [141].

Fig. 41.3 Labial herpes simplex: unilateral grouped vesicles on an erythematous base on upper lip

Fig. 41.4 Genital herpes simplex: different stages of lesions, erosion, and crusts on an erythematous base

Fig. 41.6 Chronic herpes simplex infection: large ulcers spreading from the perianal area in a severely immunosuppressed HIV patient

Fig. 41.5 Chronic herpes simplex infection: multiple polycyclic ulcers in a child with advanced AIDS

Complementary Examinations

Despite the low sensitivity and specificity, in typical presentations of HSV infection the clinical diagnosis is plausible, and the anamnesis components can be helpful: history of unprotected sexual exposure, early episodes of similar wounds at the same site, and associated general symptoms (malaise, fever, lymphadenopathy) [81, 141]. In the presence of atypical clinical presentations, which usually occur in immunosuppressed patients, laboratory tests may be necessary for a definitive diagnosis. These include viral isolation in culture, cytologic smear (Tzanck test), tissue histology, viral antigen detection, viral DNA detection by polymerase chain reaction (PCR) techniques; and type-specific serologic assays [40, 154] (Table 41.3). The Tzanck test is a simple, rapid, and inexpensive tool in clinical practice, although its sensitivity and specificity are reduced. The specimen has to be collected preferably at the base of a recent vesicle or ulcer, stained via the Giemsa, Wright, or Papanicolaou

Table 41.3 Laboratory tests for the diagnosis of herpes simplex infection

Method	Principle	Sample	Sensitivity	Specificity	Advantages	Disadvantages
Viral antigen detection	Immunoperoxidase staining	Swab; smears from lesions; vesicular fluid; exudate from base of vesicle	Middle (80%)	High (90%)	Relatively inexpensive; Rapid Integrity of the specimen not required; Typing possible	Suboptimal sensitivity
	Capture ELISA	Swab; vesicular fluid; exudate from base of vesicle	High (Genital ulcer >95%)	Variable (62–100%)	–	Fresh vesicle; No viral type
	Rapid test device		Unknown	Unknown	Point-of-care testing	–
Virus culture[a]	HSV isolation susceptible cells	Swab; skin lesions; vesicular fluid; exudate from base of vesicle; mucosal sample without lesions	Variable[e]	≈100%	"Gold standard" method; Virus typing; Resistance phenotype testing	Less sensitive than PCR; Specialized laboratories
Molecular biology[a]	HSV DNA detection/quantitation by NAAT (PCR, real-time PCR[b], and commercial assays)	Also blood for molecular biology	High (98%)	High (≈100%)	High sensitivity; Virus detection and typing in the same test; Resistance genotyping; Fast results	Specialized laboratories; Not standardized; Not validated for all samples; PCR: risk of contamination
Cytologic examination	Tzanck smears Papanicolaou or Romanovsky stain	Skin/mucosal lesions Biopsies	Low	Low	Inexpensive	Fresh lesion; No distinction between HSV1 and 2, nor VZV
	Detection of infected cells by direct immunofluorescence	Smears; tissue section; smear from base of vesicle	Middle[f]	High (>95%)	Inexpensive; Rapid (<4 h possible); Typing possible	Fresh vesicles; Suboptimal sensitivity; Time-consuming; Not standardized
Serologic tests	Western blot[c]	Serum	≈100%	≈100%	Specific of HSV-1 and HSV-2; Earliest seroconversion: 13 days	Not commercially available; Expensive
	Monoclonal antibody-blocking EIA[d]		≈100%	≈100%	Distinguish between HSV-1 and 2	Not commercially available
	ELISA		93–98%	93–99%	ELISA commercially available	May lack of sensitivity and specificity

Fatahzadeh and Schwartz [81], LeGoff et al. [154], http://doi.org/10.1186/1743-422X-11-83, Levin et al. [158]

CDC Centers for Disease Control and Prevention, *EIA* enzyme immunoassay, *ELISA* enzyme-linked immunosorbent assay, *HSV* herpes simplex virus, *NAAT* nucleic acid amplification test, *VZV* varicella zoster virus

[a] Currently the "preferred" test of CDC (2010)

[b] Real-time PCR: method of choice for skin lesions

[c] Reference ("gold standard") test proposed by University of Washington (USA)

[d] Reference ("gold standard") test proposed by the Central Public Health Laboratory in the United Kingdom

[e] Depending on lesion (vesicular content >90%; ulcer 95%; swab 70%–80%; mucosa without lesion 30%, and also on sample storage and transport conditions

[f] Genital ulcer: 70–90%; asymptomatic: <40–50%

technique, and examined through an optical microscope to identify characteristic virus-induced cytopathologic findings. The Tzanck test verifies the HSV infectious etiology or a herpes zoster etiology; it does not provide a distinction between HSV-1 and HSV-2, nor between HSV and varicella zoster virus infection. The confirmation of the causative agent is obtained through viral culture, which is the gold-standard method, or by PCR-based techniques [40, 154]. Viral culture sensitivity is lower for old, dry, crusty lesions, and in patients with recurrent infection, in contrast to primary lesions [158]. PCR-based testing has the greatest overall sensitivity and specificity. Despite its high sensitivity and specificity, culture and detection by PCR is costly, resulting in limited routine use because of the high prevalence of the virus [40].

Therapeutic Approach

Antiherpetic treatment is beneficial for most symptomatic patients, possibly helping symptom control when used during the infection's early signs and symptoms, or for recurrence suppression. Antiviral agents do not cure HSV infections, but rather modify the clinical course of the disease through the inhibition of viral replication and subsequent epithelial damage [81]. The antiherpetic drugs acyclovir, famciclovir, and valacyclovir are safely used in HIV patients [227, 228]. Acyclovir requires several doses a day because of its short half-life. Famciclovir and valacyclovir have a longer half-life, allowing fewer doses per day, which may ensure better compliance to treatment despite their higher cost. Recommendations for HSV therapy in HIV patients are summarized in the Table 41.4. Long-term suppressive therapy is indicated for patients with severe recurrences, or to minimize the frequency of recurrences or reduce the risk of genital ulcer disease (GUD) in patients with CD4 counts <250 cells/mm^3 who initiate ART [227, 228]. It is worth noting that suppressive treatment does not decrease the HSV or HIV transmission risk in HIV/HSV-coinfected patients [40]. Another important point is that the prevalence of HSV-2 shedding and GUD may increase significantly after ART initiation, possibly related to the

Table 41.4 Treatment of herpes simplex in HIV patients

Orolabial lesions (duration: 5–10 days)
Acyclovir 400 mg PO tid, or
Famciclovir 500 mg PO bid, or
Valacyclovir 1 g PO bid
Initial or recurrent genital lesions (duration: 5–10 days)
Acyclovir 400 mg PO tid, or
Famciclovir 500 mg PO bid, or
Valacyclovir 1 g PO bid
Severe mucocutaneous HSV infections
Initial therapy acyclovir 5 mg/kg IV q8h
After lesions begin to regress, change to oral therapy as above
Continue treatment until lesions have completely healed
Chronic suppressive therapy
Indications:
Patients with severe recurrences, or
Patients who want to minimize the frequency of recurrences, or
To reduce the risk of GUD in patients with CD4 cell counts <250 cells/mm^3 who are starting ART
Treatment:
Acyclovir 400 mg PO bid, or
Famciclovir 500 mg PO bid, or
Valacyclovir 500 mg PO bid
Evaluate ongoing need for suppressive therapy annually
Acyclovir-resistant mucocutaneous HSV infections
Preferred therapy:
Foscarnet 80–120 mg/kg/day IV in 2–3 divided doses until clinical response
Alternative therapy (duration: 21–28 days or longer, based on clinical response):
Topical imiquimod 5% cream three times/week, or
Topical trifluridine[a], or
Topical cidofovir[a] 1% gel, or
IV cidofovir 5 mg/kg IV once weekly

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents [227, 228]

ART antiretroviral therapy, *bid* twice daily, *GUD* genital ulcer disease, *HSV* herpes simplex virus, *IV* intravenously, *PO* orally, *q8h* every 8 h, *tid* three times a day

[a]Topical formulations of trifluridine and cidofovir are not commercially available; extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and the intravenous formulation of cidofovir.

immune reconstitution inflammatory syndrome (IRIS). ART is not associated with reduced HSV shedding in HIV coinfected adults; it may be prudent to counsel patients during early ART and

consider oral acyclovir therapy [169, 297]. Acyclovir resistance may occur mainly in immunocompromised patients, requiring treatment with intravenous drugs such as foscarnet and cidofovir. Both medications are nephrotoxic, requiring hydration and monitoring of renal function. Topical imiquimod, trifluridine, cidofovir, and intravenous cidofovir are alternative therapies.

Varicella Zoster Virus

Varicella-zoster virus (VZV) causes two diseases: varicella (chickenpox) and herpes zoster (shingles). Varicella is the clinical manifestation of the VZV primary infection, whereas herpes zoster (HZ) results from the viral reactivation.

General Epidemiology

Varicella is highly contagious, affecting younger individuals, predominantly children younger than 10 years, while HZ affects preferably adults and elders after their sixth decade, and the cutaneous manifestations lead to higher morbidity. The risk for HZ is higher among the elderly, immunosuppressed patients, and children affected by varicella in their first year of life, or whose mothers were affected by varicella during pregnancy [272]. HIV-infected adults and children, even undergoing ART, are more prone to HZ episodes than the general population, displaying incidence rates ten times higher, resulting in significant morbidity [256]. HZ may occur at any stage of the HIV infection, may be the first clinical manifestation of HIV, or may develop during the IRIS [321].

Etiopathogenesis

VZV is an enveloped large DNA neurotropic virus, an alpha-herpes virus (family Herpesviridae) consisting of a single serotype, with humans as the specific reservoir [158, 272]. VZV causes two forms of clinical presentation: varicella and herpes zoster. The vesicular lesions have high viral concentrations and can result in primary infection in susceptible hosts. The contagious period transitions from vesicle development to crust formation [116]. VZV is cytopathogenic during the productive infection, although it establishes latency after the primary infection (varicella). Following centripetal axonal transport, viral DNA persists in neurons of dorsal root and cranial nerve ganglia, where it can remain quiescent for years. From there the virus can be reactivated and, after centrifugal transport via nerve axons, can cause recurrent infections that represent HZ [272].

Clinical Presentation

Vesicle formation is the hallmark of both types of VZV infection [158]. Varicella starts as a prurignous vesicular exanthema with disseminating lesions displaying varied evolutionary stages (papules, vesicles, and crusts) (Fig. 41.7), although more prevalent on the face and trunk. In HZ vesicular or bullous lesions can be painful, and their presentation is unilateral and segmental along a cutaneous region innervated by the impaired sensory ganglion (dermatome) [124]. Less frequently, two or more dermatomes may be
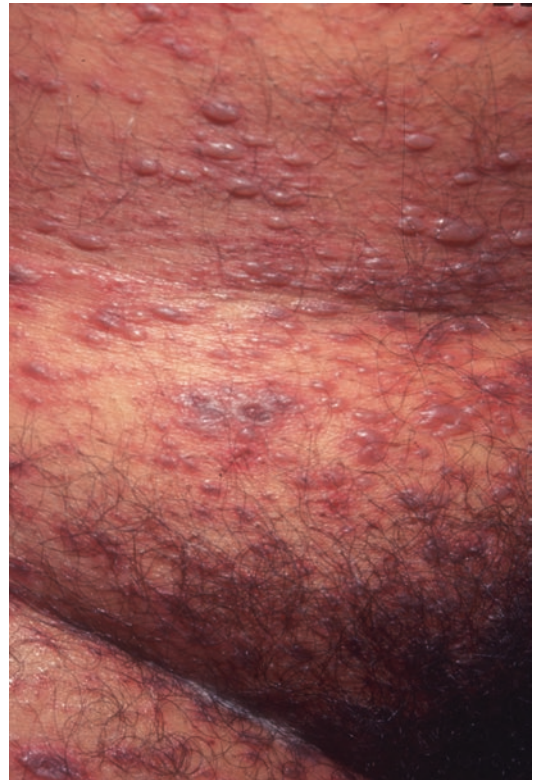
Fig. 41.7 Varicella: varied lesion stages with disseminated hemorrhagic vesicles, blisters, and some crusts

affected. When more than three dermatomes are involved, or more than 20 lesions develop from the early impaired dermatome, disseminated HZ is characterized (Fig. 41.8) [124, 321]. The most affected dermatomes are those corresponding to the thoracic and cervical ganglia, and the ophthalmic branch of the trigeminal nerve (Fig. 41.9).

Fig. 41.8 Herpes zoster: severe herpes zoster affecting at least four dermatomes

Fig. 41.9 Ophthalmic herpes zoster: unilateral ulcerated lesions and crusts affecting the ophthalmic division of the trigeminal nerve

Fig. 41.10 Herpes zoster Ramsay Hunt syndrome: ipsilateral facial paralysis, ear pain, and vesicles in the auditory canal and auricle

In HIV-infected patients, HZ may display atypical lesions, e.g., follicular, ecthyma-like, ulcerated, crusty, verrucous, or hypertrophic. In HIV-infected children the primary infection can be severe and fatal, with systemic dissemination (pneumonitis, pancreatitis, and encephalitis). Extracutaneous involvement can also occur in adults, leading to higher morbidity and mortality. The major otologic complication of VZV reactivation is the Ramsay Hunt syndrome, which typically includes the triad of ipsilateral facial paralysis, ear pain, and vesicles in the auditory canal and auricle (Fig. 41.10) [98]. HZ may also be a manifestation of the immune reconstitution syndrome, developing after the start of ART, usually in patients with increased viral load and decreased CD4 count [124].

Complementary Examinations

Varicella and HZ diagnoses are clinical, mainly based on history and clinical picture; specifically the appearance of the skin eruption and characteristic location, in association with localized pain. Diagnosis verification through laboratory tests are

usually less useful, since most of the tests are time consuming, have low specificity, or are not routinely available. Nevertheless, in selected patients, mainly the immunocompromised, HZ presentation can be atypical and require confirmatory tests for the precise diagnosis [158, 272]. The available laboratory tests include Tzanck smear, direct immunofluorescence, viral culture, PCR, and serology. Tests providing quicker results are the Tzanck smear and direct immunofluorescence; the former does not distinguish VZV from other herpesvirus infections. Immunofluorescence distinguishes both infections and is more sensitive than culture, although less sensitive than PCR techniques. PCR is the most appropriate test because of its high sensitivity and specificity. Culture is highly sensitive, although its time-consuming profile does not qualify the test for timely antiviral therapy [158, 272].

Therapeutic Approach

First-line antiviral therapy is based on antiviral nucleoside analogs (acyclovir, valacyclovir, famciclovir), and comparative trials do not support the efficacy of one over the other. The treatment aims include scarring acceleration, decreasing lesion progression, promoting efficient analgesia and preventing complications, such as postherpetic neuralgia and secondary infections. Early administration may reduce tissue damage, and, consequently, the destruction of affected ganglion cells in HZ can be diminished or even prevented [272]. The oral route is used for mild cases not associated with immunodeficiency. For severe disease, central nervous system (CNS) involvement, disseminated HZ, and HZ associated with impaired immune system, the intravenous route is indicated [158, 272]. Table 41.5 summarizes the antiviral treatment for HZ.

Systemic antiviral treatment is recommended for all HIV-infected patients, including children and pregnant women, regardless of their immunologic status, and even if they present after 72 h [321]. Patients with disseminated HZ should be hospitalized for intravenous acyclovir therapy. VZV/HIV-coinfected patients should be treated until all lesions have healed, which is often longer than the standard 7- to 10-day course [75]. Many approaches can be used for HZ acute pain management, including paracetamol, anti-inflammatory nonsteroidal drugs, tricyclic antidepressants, opiate derivatives, capsaicin, and topical anesthetics [116]. To treat postherpetic neuralgia (PHN; pain lasting longer than 1 month), tricyclic antidepressants or anticonvulsants can be combined with analgesics [124, 199]. Table 11.5 in Chap. 11 lists drugs and doses for the treatment of PHN. For HIV patients with early exposure to VZV, the use of a specific immune globulin over the first 96 h (Table 11.4, varicella zoster immune globulin) is recommended, or oral antiviral treatment over 7 days after exposure [124]. Administration of varicella vaccine is not recommended in HIV-infected patients with severe immunosuppression (CD4 cell percentage <15% or, if older than 5 years, a CD4 count <200 cells/mm^3). Zoster vaccine is not recommended in HIV-infected patients with a CD4 cell count <200 cells/mm^3, and there is no consensus about zoster vaccine for patients with higher CD4 counts [143].

Table 41.5 Antiviral treatment for varicella and herpes zoster

Antiviral drug	Antiviral dose[a]	Administration	Indication
Acyclovir	800 mg 5×/day	Orally	Zoster, varicella in risk patients
–	10 mg/kg q8h	IV	Severe and generalized VZV infections, HZ associated with immunosuppression
Valacyclovir	1 g tid	Orally	Varicella and herpes zoster
Famciclovir	500 mg tid	Orally	
Brivudin	125 mg qd	Orally	
Foscarnet	40 mg/kg q8h	IV	VZV infections caused by TK-negative VZV strains

Dworkin et al. [75] and Sauerbrei [272]
bid twice daily, *IV* intravenously, *q8h* every 8 h, *qd* once a day, *tid* three times a day
[a]VZV disease in HIV-infected patients should be treated until all lesions have healed

Molluscum Contagiosum

General Epidemiology

Molluscum contagiosum (MC) is a frequent cutaneous viral infection with an estimated prevalence of 2–8% in the general population. In HIV-positive patients the prevalence reaches up to 33% in patients with a CD4 count <100/mm^3 [175]. MC development clearly indicates progression of the HIV-associated disease [209]. Despite the sizable impact ART has made on the prevalence of dermatologic disease, MC remains an important cause of morbidity in HIV-positive populations.

Etiopathogenesis

MC is an infection caused by the molluscum contagiosum virus, a DNA virus member of the *Molluscipoxvirus* genus, in the Poxviridae family [175]. Transmission occurs through skin-to-skin contact with infected persons, including through sexual intercourse, by fomites (towels, pools), or autoinoculation. The incubation period ranges from 7 days to 3 months and transmission occurs as long as there are active lesions [175, 221].

Clinical Presentation

MC presents with white, painless papules with central umbilication (Fig. 41.11). In immunosuppressed HIV patients, this condition tends to be more severe and widespread, and classical lesions can be large (>1 cm), confluent, and disfiguring, particularly when the CD4 count is <200 cells/mm^3. Persistent, recurrent, and disseminated lesions with abrupt onset can also occur [209]. The lesions can develop on any body part, although in the HIV patient they mainly affect the genital region and the face [198]. The diagnosis is essentially clinical, based on the morphologic characteristics, although atypical presentations may require histopathologic examination for diagnosis definition [124]. Fungal diseases, such as histoplasmosis and cryptococcosis, are differential diagnoses to be considered in the immunosuppressed patient with molluscum-like lesions [199].

Complementary Examinations

Complementary examinations are usually not required. Investigation of immunodeficiency is

Fig. 41.11 Molluscum contagiosum: pearl-like papules with central umbilication on the face

suggested in atypical presentations. For histologic analysis, the specimen can be obtained by curettage of one or more MC lesions, as well as biopsy. Histologically, MC virus infection is characterized by epidermal hyperplasia with accelerated keratinization and the presence of cytoplasmic inclusion bodies, known as Henderson–Patterson bodies, which displace the nucleus and flatten it against the cell membrane. These inclusion bodies are pathognomonic of the disease [175].

Therapeutic Approach

Given the poor quality of studies and evidence, no specific recommendation can be made for the treatment of MC in HIV-infected individuals other than the initiation of ART [175]. Besides ART initiation that induces immune system recovery, complementary therapy may be necessary for clinical resolution of the lesions. Pharmacologic topical treatment includes retinoids, imiquimod, potassium hydroxide, cantharidin, salicylic acid, and podophyllotoxin.

Nonpharmacologic options consist of destructive techniques and include cryotherapy, curettage of individual lesions, and electrodesiccation [306]. The choice is dependent upon the location and extension of the lesions, skin phototype, resource availability, and the clinician's experience with the technique. Possible complications such as dyschromia and scarring sequelae have to be also considered regarding the therapeutic choice. Topical treatments with tretinoin, podophyllotoxin, and imiquimod can be an alternative when there are many lesions [124, 199].

Oral Hairy Leukoplakia
Oral hairy leukoplakia (HL) is a benign mucous disease related to immunosuppression, indicative of disease progression to AIDS in HIV-positive individuals [101].

General Epidemiology
HL occurs in around 25% of HIV-infected adults, possibly developing at any stage of the HIV infection, although it affects mainly patients with low counts of CD4 and high viral load [198, 255]. The HL/HIV coinfection has epidemiologic significance: HL may be an indicator of HIV infection and predicts HIV disease progression, has been used as a criterion for initiation of ART, has been used in clinical staging and classification systems, correlates with HIV viral load, usually decreases with ART, and recurs as ART fails [101].

Etiopathogenesis
The infection is caused by the Epstein–Barr virus (EBV). In the immunosuppressed patient the viruses proliferate in the epithelial cells of the oral mucosa and the tongue [255]. The pathogenesis of HL is not entirely clear. EBV from saliva, circulating B lymphocytes or monocytes, or latent within-tongue epithelium may replicate under the influence of suppressed anti-EBV cell-mediated immunity, causing typical HL lesions [101].

Clinical Presentation
The clinical appearance of HL involves white or gray plaques of varying size, usually on the lateral border of the tongue or other areas of the oral mucosa, which may show vertical corrugations

Fig. 41.12 Oral hairy leukoplakia: white linear papules on the lateral border of the tongue

and cannot be rubbed off (Fig. 41.12). They are mostly asymptomatic [101, 232]. The differential diagnosis includes oral white lesions, such as idiopathic leukoplakia, smoking-associated leukoplakia, dysplasia, squamous cell carcinoma, hyperplastic candidiasis, and lichen planus [101].

Complementary Examinations
The histopathologic assessment displays hyperkeratosis, acanthosis with superficial edema, koilocytes on the spinous layer, and absence of inflammation. The definitive diagnosis can be obtained through EBV demonstration through in situ hybridization or PCR [198]. The diagnosis can be verified by EBV identification through in situ hybridization techniques, PCR, and electron microscopy [209].

Therapeutic Approach
HL is usually asymptomatic and has a nonmorbid nature, and generally no treatment is needed. HL may improve or resolve with topical podophyllum and tretinoin [232]. The lesions improve when ART is introduced, leading to recovery of the immunologic status [198, 209].

Human Papillomavirus
Human papillomaviruses (HPV) are a large group of double-stranded DNA viruses widely distributed among humans. HPV-associated diseases include anogenital and other mucocutaneous warts as well as cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancers [231].

General Epidemiology

Infection with cutaneous HPV types is ubiquitous and cutaneous warts are common in children, with a peak incidence during adolescence and declining thereafter. Warts are spread via person-to-person contact or indirectly by fomites [202, 216]. The prevalence of cutaneous common warts in HIV-infected individuals is about 18%, in contrast with 1–2% in noninfected patients [96]. Anogenital warts are a common worldwide public health problem, and sexual behavior is a primary risk factor associated with anogenital and oral HPV infection among men and women, since anogenital HPV is primarily transmitted through vaginal, anal, and oral intercourse [216]. It is estimated that more than 50% of sexually active persons become infected with anogenital HPV during their lifetime, with a peak incidence between the ages of 20 and 24 years old [40]. Despite the introduction of ART, there is evidence that eradication of anogenital HPV infection is especially difficult in patients with a CD4 count <50 cells/mm^3 [182].

Etiopathogenesis

HPV is a group of nonenveloped double-stranded DNA viruses of which at least 150 genotypes have already been identified. HPV is tissue specific, with approximately 40 types known to infect the anogenital region and oral cavity, whereas multiple HPV types are responsible for cutaneous warts [216]. Genotypes are divided into low-risk (nononcogenic) and high-risk (oncogenic), and affect the skin and the mucosae [40]. Low-risk HPV 6 and 11 account for 90% of anogenital warts. High-risk HPV 16 and 18 have oncogenic potential, and underlying immunosuppression is associated with more rapid progression of the premalignant lesions of low and high grades [68, 96]. The interaction between HPV and HIV is complex: HPV causes greater susceptibility to the acquisition of HIV, and HPV/HIV coinfection reduces the HPV clearance. As a result of such counterplay, HIV-infected patients are at increased risk of developing anal and cervical cancers, as well as vulvar and penile carcinomas [254]. Oral and genital warts have been observed in HIV patients receiving ART as part of the IRIS [190].

Clinical Presentation

Warts are benign epithelial skin tumors, usually classified into anogenital and nonanogenital warts. The lesions are mostly self-limited, asymptomatic, or subclinical. The different HPV subtypes are associated with varied clinical presentations. Nonanogenital cutaneous warts are asymptomatic verrucous papules, located at any body part [202]. Common warts (verruca vulgaris) are the most often seen, presenting as papular or nodular, keratotic lesions that display dark points on their surface, corresponding to thrombosed capillary loops (Fig 41.13). They are usually seen on the hands (Fig. 41.14), plantar regions, elbows, and knees. Filiform warts resemble keratotic spicules, usually on the face and neck (Fig. 41.15). Deep plantar warts can be less noticeable and very painful. Flat warts (plane warts or verruca plana)

Fig. 41.13 Common warts: hyperkeratotic papules with tiny dark points on their surface, corresponding to the thrombosed capillary loops

Fig. 41.14 Common warts: yellowish hyperkeratotic palmar papules

Fig. 41.15 Filiform warts: keratotic papules and spicules on the face

Fig. 41.16 Genital warts: hyperkeratotic papules on the penis with papillomatous lesion in the distal portion

are flat or slightly elevated flesh-colored papules, measuring 1–5 mm wide, frequently numerous on the face and hand dorsum. Anogenital warts, or condyloma acuminatum, are the more common presentation of sexually transmitted HPV infection. HPV causes a multifocal infection of the anogenital skin, lesions being most common at the site of trauma during sexual intercourse, but may occur at any genital or perigenital site [52]. Clinically they are papules, nodules, or plaques, usually asymptomatic (Figs. 41.16 and 41.17).

Fig. 41.17 Anal warts: large vegetating plaques in the perianal area

Complementary Examinations

The diagnosis is clinical, although biopsy can be performed for atypical or treatment refractory lesions. Since anogenital warts can be sexually transmitted, an appropriate screen for other sexually transmitted infections (STIs) is recommended.

Therapeutic Approach

Up to 30% of genital warts will spontaneously regress; however, recurrence is common [216]. Treatment is directed to the visible lesions caused by HPV, and no therapy modalities are curative. Treatment regimens are classified as either patient-applied or provider-administered modalities. Table 41.6 lists the main therapeutic options for external anogenital warts. Therapies for nonanogenital warts are addressed in Chap. 11. There is little evidence to support the unequivocal choice of the best treatment for cutaneous and mucosal warts. All treatments have significant failure and recurrence rates. Data from systematic reviews and economic evaluation of interventions for the treatment of genital warts have suggested that ablative techniques seem to have better primary clearance rates despite their higher cost-effectiveness [148, 299]. The potential advantages and disadvantages of the individual treatments must be considered, and therapeutic choice should be based on location, size and number of lesions, adverse reactions associated with therapy, cost, patient preferences, comorbidities and age; and provider experience. If 3 months of

Table 41.6 Therapeutic options for external anogenital warts

	Treatment	Regimen	Adverse effects	Comments
Patient-applied	Imiquimod[a] 5% **OR** Imiquimod[a] 3.75%	Once at bedtime, three times a week for up to 16 weeks	Local inflammation, itching burning, vesicles, erosions, ulcers, crusting, local sclerosis dyschromia	Not suitable for pregnant women
		Once at bedtime, daily, for up to 8 weeks		
	Podophyllotoxin 0.5% solution or gel	Twice a day for 3 consecutive days, followed by 4 days of no therapy, for up to four cycles	Local inflammation, erythema, itching, pain, erosions	Total wart area treated should not exceed 10 cm^2
				Total volume of podophyllotoxin should be limited to 0.5 mL per day
				Contraindicated for pregnant women
Provider-administered	Cryotherapy (liquid nitrogen)	Weekly or every other week	Pain, local inflammation, bullae, ulcer, necrosis	It can be used in pregnant women
	TCA 80–90% solution	Weekly	Pain, burning	It can be used in pregnant women
	Podophyllin resin solution 10–25%	Weekly	Local inflammation, pain, ulcer	Total wart area treated should not exceed 10 cm^2
				Total volume should be limited to 0.5 mL per day
				Contraindicated for pregnant women
	Surgical removal[b]	–	Pain, scarring	–
	Laser (CO$_2$ or Nd:YAG)	–	Pain, scarring	High cost

CDC [40], Clinical Effectiveness Group [52], Kollipara et al. [144], Lacey et al. [148], Park et al. [231], Steben and Garland [293]

TCA trichloroacetic acid

[a]Latex condoms may be weakened if in contact with imiquimod

[b]Either by tangential scissor excision, tangential shave excision, curettage, or electrosurgery

any treatment does not yield improvement, a new therapy should be attempted [40, 144]. Soft nonkeratinized warts respond well to podophyllotoxin and trichloroacetic acid (TCA). Keratinized lesions may be better treated with physical ablative methods such as cryotherapy, excision, TCA, or electrosurgery. Imiquimod is suitable treatment for both keratinized and nonkeratinized warts [52]. HIV patients with impaired cell-mediated immunity may show lower response and higher recurrence rates, eventually requiring combined therapies [52]. Counseling for condom use is highly advisable. Condoms used consistently and correctly can lower the chances of acquiring and transmitting HPV; however, because HPV can infect areas not covered by a condom, condoms might not fully protect against HPV [40]. A vaccine is available for males and females to prevent genital warts. HPV vaccine is recommended routinely for boys and girls aged 11–12 years, as well as for young men through age 21 years and young women through age 26 years who have not previously been vaccinated. HPV vaccine is also recommended for MSM, persons living with HIV/AIDS, and immunocompromised persons through age 26 years. HPV bivalent and quadrivalent vaccines are recommended for girls/women, whereas only HPV quadrivalent vaccine is recommended for boys/men [40, 171].

Acquired Epidermodysplasia Verruciformis

Epidermodysplasia verruciformis (EV) is a rare autosomal recessive genodermatosis characterized by a defect in cell-mediated immunity and increased susceptibility to infections increased susceptibility to specific HPV genotypes infection. There are more than 20 known HPV types associated with EV (EV-HPV) [137, 260]. Acquired epidermodysplasia verruciformis (AEV) is a rare disease observed in patients with impaired cell-mediated immunity and predisposition to HPV infection, mainly described in HIV patients [260, 330]. The main clinical features of AEV are similar to EV: a rash resembling pityriasis versicolor and flat warts (Fig. 41.18a). The rash consists of a widespread papular eruption of reddish to skin-colored, hypopigmented, gray, brown, flat, wart-like lesions mostly involving the sun-exposed areas of the skin. Local trauma may induce the isomorphic (Koebner) phenomenon to produce a linear distribution of papules (Fig. 41.18b). They usually present as multifocal lesions ranging in size from millimeters to centi-

meters. In the last decade, several cases of acquired EV have been reported, particularly in HIV-infected patients [137]. It seems that AEV is more frequent in young, vertically HIV-infected patients than in adults infected later in life [164]. In HIV disease, proliferation of lesions is associated with progressive immunosuppression or during IRIS after initiation of ART [131, 308]. Selected EV-HPV strains appear to have a substantial link with oncogenic transformation [131, 308]. Despite this relationship, the role of HPV in the development of AEV lesions and the eventual malignant transformation of these lesions is not known. At present there is no known effective treatment for AEV in HIV patients [330]. Anecdotal reports have shown attenuation of warts with topical glycolic acid [193] or even clearance with topical cidofovir [67]. The detection of high risk HPV types on the skin lesions of HIV-infected children with AEV supports the need for a continuous follow-up, as the long-term cutaneous cancer risk in these patients remains unknown [164, 308].
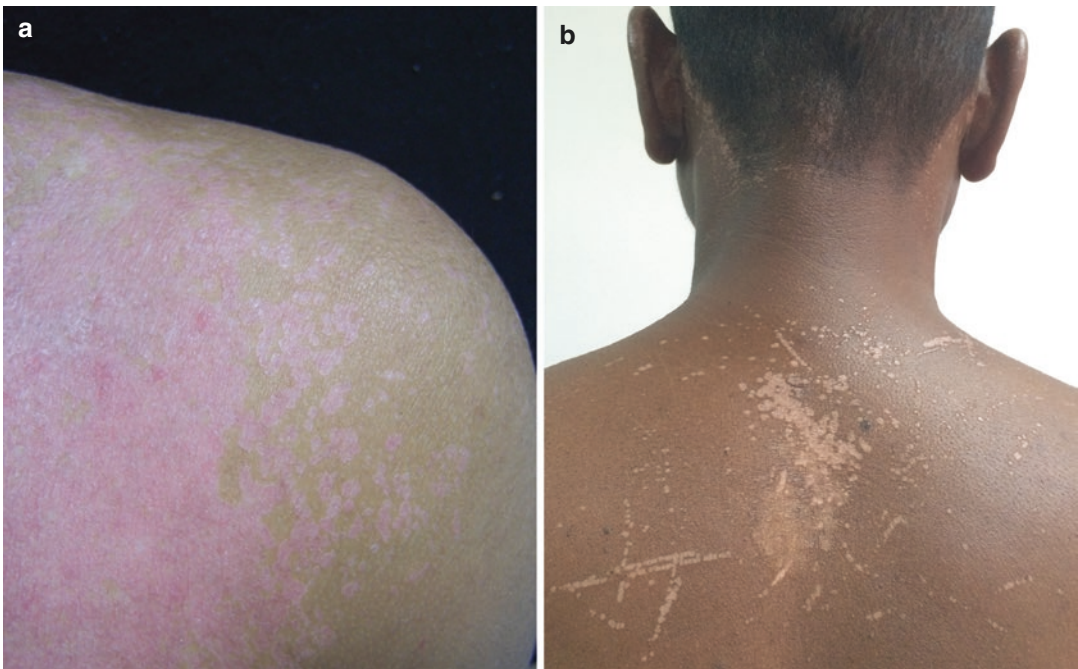
Fig. 41.18 Epidermodysplasia verruciformis. (**a**) Widespread hypopigmented papular eruption resembling pityriasis versicolor. (**b**) Linear distribution of papules induced by local trauma (isomorphic [Koebner]) phenomenon

Bacterial Diseases

Cutaneous Bacterial Infections

General Epidemiology

The most common bacterial infections in HIV-infected patients result from *Staphylococcus aureus* and *Streptococcus pyogenes* [9]. *S. aureus* nasal colonization rate in HIV-infected patients is about 50%, twice the rate observed in non-HIV-infected. Methicillin-resistant *S aureus* infection should also be considered in HIV-infected patients [198, 256, 298].

Etiopathogenesis

The largest amount of cutaneous and systemic bacterial infections observed in HIV patients is multifactorial: frequent nasal colonization by *S. aureus*; cutaneous barrier impairment, and immunologic dysfunction of T and B lymphocytes, neutrophils, and macrophages [198, 298]. Use of venous catheters as well as pruritus, which favor skin microtraumas, also play a role in cutaneous lesion development [298].

Clinical Presentation

The clinical manifestations are varied, and impetigo (Fig. 41.19), folliculitis, furuncle (Fig. 41.20), abscess, ecthyma, and cellulitis are the most often found presentations [9, 298]. The lesions are usually localized on the lower limbs, gluteal region, and scrotum, although they may have a locally aggressive course, eventually evolving into bacteremia and sepsis [209].

Complementary Examinations

Diagnosis is based on clinical findings. Direct examination and culture of smears and tissues, as well as histopathologic study, should be performed as needed [198]. Scrapes from superficial lesions can be examined under a microscope using the Gram technique. Collection of samples from cutaneous lesions and nasal mucosa is recommended for recurrent infections and deeper lesions in order to assess the bacteriologic profile and conduct and antibiogram [96, 298].

Fig. 41.19 Impetigo: inflammatory superficial weeping lesions covered by orange crusts

Fig. 41.20 Furuncle: erythematous nodule with spontaneous drainage of purulent secretion on the armpit

Therapeutic Approach

The treatment is similar for HIV-infected and noninfected patients, with a recommendation for therapy maintenance until complete remission. Systemic semisynthetic penicillins or cephalosporins are usually effective for superficial lesions. Abscesses should be drained with surgical incision or needle aspiration, and samples may be used for microbiological assessment

(Gram staining, culture, and antibiogram). For patients with recurrent infections, decolonization of *S. aureus* chronic carriers can be achieved with topical nasal mupirocin [96, 298].

Syphilis

Syphilis is an STI caused by the spirochete bacteria *Treponema pallidum*. A myriad of mucocutaneous and systemic manifestations can be present in different stages (primary, secondary, latent, and tertiary syphilis). Transmission is higher during primary and secondary stages of the infection.

General Epidemiology

Syphilis and HIV overlap and interact in a number of significant ways. They share common risk factors, are sexually transmitted, and can be transmitted vertically to a child or fetus. Syphilis increases the risk of HIV transmission, and HIV infection can alter the natural history of syphilis [240, 294]. While anyone who has sex can contract an STI, sexually active gay, bisexual, and other MSM are at increased risk for STIs; other risk factors for syphilis acquisition include history of early STI, multiple sexual partners, and practices of unprotected oral sex [40, 183, 322]. Rates of primary and secondary syphilis progressively declined from 1990 to 2000 whereas since 2000, an increase in syphilis incidence has been observed worldwide [239, 294].

Etiopathogenesis

In acquired syphilis the disease results from the infection with *T. pallidum* bacteria which penetrate through tiny abrasions during sexual contact. Congenital syphilis is a severe, disabling, and often life-threatening infection seen in infants. A pregnant mother who has syphilis can spread the disease through the placenta to the fetus or at birth. Blood transfusion and indirect transmission via contaminated items or tattoos are rare forms of syphilis transmission [15].

Clinical Presentation

The protean clinical presentations of syphilis earned it the name of the "Great Mimicker." The course of disease comprises primary, secondary,

Fig. 41.21 Primary syphilis (chancre): eroded indurated papule, well delimited, with smooth and clean surface

latent, tertiary, and neurosyphilis [235]. In primary syphilis an asymptomatic mucosal or skin lesion (chancre) appears 3 weeks after the initial exposure at the point of contact and usually heals spontaneously after 4–6 weeks (Fig. 41.21). Local lymph node swelling can occur [235]. Typical signs of secondary syphilis are localized or diffuse symmetric mucocutaneous lesions and generalized nontender lymphadenopathy. Lesions are symmetric, slightly erythematous macules and papules (syphilids) measuring up to 10 mm in diameter and are distributed on the trunk, proximal extremities, palms, and soles (Fig. 41.22). Syphilids involving hair follicles may result in patchy alopecia (Fig. 41.23). In some patients, highly infectious papules develop at the mucocutaneous junctions and become hypertrophic in moist intertriginous areas (condylomata lata). General symptoms include fever, sore throat, malaise, weight loss, headache, and meningismus [235]. Latent syphilis is defined as a stage of infection caused by *T. pallidum* in which organisms persist in the body of the infected person without causing symptoms or signs, and has two subcategories. Latent syphilis acquired within the preceding year is referred to as early latent syphilis; all other cases are late latent syphilis or syphilis of unknown duration [41]. Tertiary syphilis is slowly progressive, usually occurring 1–10 years after the initial infection, and may affect any organ. The dermatologic picture is characterized by the presence of soft tumor-like gummas, which are indurated, nodular, papulosquamous, or ulcerative lesions that form characteristic circles or arcs. Besides the

Fig. 41.22 Secondary syphilis. (**a**) Scaling rash on the palms, resembling psoriasis; (**b**) syphilids on the face; (**c**) plaques and nodules in an immunosuppressed HIV patient; (**d**) syphilitic roseola, maculopapular rash on the chest

Fig. 41.23 Secondary syphilis: patchy alopecia due to involvement of hair follicles

skin, gummas may appear almost anywhere in the body including the bones [235]. Neurosyphilis may occur at any stage of syphilis, and approximately 35–40% of persons with secondary syphilis have asymptomatic CNS involvement [69]. The natural course of syphilis may be altered in HIV-infected patients, although in most cases the manifestations remain typical. In immuno-suppressed syphilis/HIV-coinfected patients, syphilis may have atypical features: a shorter incubation period, a persistent and painful primary lesion overlapping the secondary stage, multiple extragenital primary lesions, high risk for neurologic and systemic involvement, and rapid progression to secondary and tertiary stages [240, 294]. Syphilis/HIV-coinfected patients may develop so-called malignant syphilis, a rare and severe variant of secondary syphilis characterized by large papular, nodular, and ulcerative lesions covered with thick crusts affecting the trunk, the extremities, and even the face [312]. According to a large multicenter

retrospective study, concurrent HIV infection increases the risk of developing malignant syphilis by 60-fold [283].

Complementary Examinations

Careful history, sexual risk assessment, and physical examination are valuable information whenever STI patients are evaluated (Box 41.4). Laboratory tools to assess syphilis diagnostic in HIV-infected and noninfected patients are the same. Definitive diagnosis of early syphilis is made through visualization or identification of *T pallidum* spirochetes on dark-field microscopy, through direct fluorescent antibody tests, or with PCR techniques; however, these methods are routinely impractical [18, 294]. A presumptive diagnosis of syphilis is achieved by using serologic tests. Two types of serologic tests are used: nontreponemal (diagnostic) tests including the Rapid Plasma Reagin (RPR) test and the Venereal Disease Research Laboratory (VDRL) test, and the treponemal (confirmatory) tests including the fluorescent treponemal antibody absorption (FTA-ABS) test, the microhemagglutination test for antibodies to *T. pallidum* (MHA-TP), and the *T. pallidum* particle agglutination assay. Nontreponemal tests correlate with disease activity, are reported quantitatively, and are used to monitor treatment response. After treatment, nontreponemal titers typically become negative while treponemal tests remain positive throughout life [18, 40]. Both treponemal and nontreponemal tests can have false-positive results secondary to medications, and autoimmune conditions. Although uncommon, there have been sporadic reports of seronegative syphilis in HIV-infected patients. The false-negative serologic tests are generally due to the prozone phenomenon, which can occur when very high titers of antibodies interfere with the assay, and can be excluded by testing diluted serum [294]. All patients with suspected syphilis should be tested for HIV infection and screened for other STIs. Diagnostic issues are summarized in Boxes 41.5 and 45.6.

Box 41.4 Evaluating Patients for Primary and Secondary Syphilis

Sexual history, risk assessment, and physical exam

Sexual history, risk assessment (past year):	Physical examination
Gender of partners	Oral cavity
Number of partners (new, anonymous, serodiscordant HIV status, exchange of sex for drugs or money)	Lymph nodes
	Skin
Types of sexual exposure	Palms and soles
Recent STIs; HIV serostatus	Neurologic
Substance abuse	Genitalia/pelvic
Condom use	Perianal
History of syphilis prior syphilis (last serologic test and last treatment)	

All patients with suspected syphilis should be tested for HIV infection and screened for other STIs. Repeat HIV testing of patients with secondary syphilis 3 months after the first HIV test if the first test is negative

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Box 41.5 Diagnostic Issues in Primary Syphilis

Dark-field

~80% sensitive, varies with experience/skill of examiner and decreased sensitivity as lesion ages.

RPR/VDRL

- A negative RPR/VDRL does not exclude the diagnosis of syphilis; only ~75–85% sensitive in primary syphilis
- Tests must be quantified to the highest titer, and titer on the day of treatment must be used to assess treatment response
- Always use the same testing method (RPR or VDRL) in sequential testing; cannot compare titer from two different tests
- Tests lack specificity (biological false positive); all reactive tests need to be confirmed by a treponemal test for syphilis diagnosis

Box 45.6 Diagnostic Issues In Secondary Syphilis

RPR/VDRL

- ~100% sensitive in secondary syphilis
- Tests must be quantified to the highest titer, and titer on the day of treatment must be used to assess treatment response
- Always use the same testing method (RPR or VDRL) in sequential testing; cannot compare titer from the two tests
- Tests lack specificity (biological false positive); all reactive tests need to be confirmed by a treponemal test for syphilis diagnosis
- Prozone reaction: false-negative RPR or VDRL from excess antibody blocking the antigen–antibody reaction
    - ~1% of secondary syphilis cases
    - Request lab to dilute the serum to at least 1/16 to rule out

Therapeutic Approach

Penicillin via the parenteral route is the drug of choice to treat all clinical phases of syphilis [40, 323]. Treatment regimens for syphilis are shown in Table 41.7. No proven alternatives to penicillin are available for treating neurosyphilis, congenital syphilis, or syphilis in pregnant women. Parenteral penicillin G is the only therapy with documented efficacy for syphilis during pregnancy. Pregnant women with syphilis in any stage who report penicillin allergy should be desensitized and treated with penicillin [40]. The Jarisch–Herxheimer reaction is a transitory acute febrile reaction frequently accompanied by headache, myalgia, fever, and exacerbation of cutaneous lesions that can occur within the first 24 h after the initiation of any therapy for syphilis. Antipyretics can be used to manage symptoms [23]. Clinical and serologic follow-up should be performed at 6 and 12 months after treatment [40]. If, at any time, clinical symptoms develop or a sustained (>2 weeks) four-fold or greater rise in nontreponemal titers occurs, a cerebrospinal fluid (CSF) examination should be

Table 41.7 Treatment for syphilis

Clinical stage	Adults and adolescents	Infants and children	Alternative treatment for penicillin-allergic pregnant women[c, d]	Alternative treatment for penicillin-allergic nonpregnant patients
Primary, secondary, and early latent syphilis[a]	Benzathine penicillin G, 2.4 million units IM in a single dose (total 2.4 million units)	Benzathine penicillin G, 50.000 units/kg IM, up to the adult dose in a single dose	Erythromycin 500 mg PO, qid for 14 days	*CDC recommendation* Doxycycline, 100 mg PO, bid
			OR	**OR**
			Ceftriaxone 1 g IM qd for 10–14 days	Tetracycline, 500 mg PO, qid, each for 14 days
			OR	
			Azithromycin 2 g once PO	*WHO recommendation*
				Doxycycline, 100 mg PO bid or ceftriaxone 1 g IM qd for 10–14 days
Late latent syphilis[b] and unknown duration	Benzathine penicillin G 2.4 million units IM, 3 doses, 1 week apart (total 7.2 million units)	Benzathine penicillin G 50,000 units/kg IM, up to the adult dose, 3 doses, 1 week apart	Erythromycin 500 mg PO, qid for 30 days	*CDC recommendation*
				Doxycycline, 100 mg PO, bid
				OR
				Tetracycline, 500 mg PO, qid, each for 28 days
				WHO recommendation
				Doxycycline, 100 mg PO, bid for 30 days

Table 41.7 (continued)

Clinical stage	Adults and adolescents	Infants and children	Alternative treatment for penicillin-allergic pregnant women[c, d]	Alternative treatment for penicillin-allergic nonpregnant patients
Neurosyphilis	Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV q4h or continuous infusion, for 10–14 days			Procaine penicillin G 2.4 million units IM qd
				PLUS
				Probenecid 500 mg PO, qid, both for 10–14 days

CDC [40] and WHO [323]

bid twice daily, *q4h* every 4 h, *qd* once a day, *qid* four times a day, *IV* intravenously, *IM* intramuscularly, *PO* per os (oral administration)

[a]Disease acquired in the last 12 months

[b]Any case that do not fall as early latent and those of unknown duration

[c]Table shows WHO recommended regimen; according to CDC guidelines, pregnant women with syphilis in any stage who report penicillin allergy should be desensitized and treated with penicillin

[d]Erythromycin and azithromycin do not cross the placental barrier completely; it is therefore necessary to treat the newborn infant soon after delivery

performed and treatment administered accordingly. If the nontreponemal titer does not decline four-fold after 24 months, CSF examination can be considered and treatment administered accordingly, although initial low titers (<1:8) might not decline [40].

Bacillary Angiomatosis

Bacillary angiomatosis (BA) is a vascular, proliferative form of *Bartonella* infection that occurs primarily in immunocompromised patients.

General Epidemiology

BA is traditionally seen in HIV-infected patients with advanced disease, with CD4 count <100 cells/mm^3 [192].

Etiopathogenesis

The infection results from the Gram-negative *Bartonella quintana* and *Bartonella henselae* bacteria. Humans are the reservoir of the bacterium, and the human body louse, *Pediculus humanus corporis*, is its usual vector. Body lice are probably not the only vectors of *Bartonella*. The transmission of *Bartonella* to humans may also result from cat scratch involving the claw of a cat that is contaminated with *Bartonella*-infected flea feces [73, 86].

Clinical Presentation

There are two distinct *Bartonella*-associated syndromes: bacteremia (in the absence of focal tissue vascular proliferative response) and the tissue infection (BA) associated with angiogenic response. Bacteremia can systemically spread *Bartonella*, mainly to the liver (hepatic peliosis) and the spleen [86]. Angioproliferative lesions are generally cupuliform papules which may also present as nodules or friable and easily bleeding erythematous-violaceous plaques (Fig. 41.24). They may vary in number, from solitary to thousands of lesions, and sized 1 mm to many centimeters. Lesions may also be subcutaneous nodules, masses, or cysts [192]. Vascular cutaneous lesions, such as hemangiomas, pyogenic granuloma, angiosarcoma, and Kaposi's sarcoma, should be borne in mind as the main differential diagnoses.

Fig. 41.24 Bacillary angiomatosis: erythematous friable nodules on the foot

Complementary Examinations

Skin biopsy, serologic tests, and peripheral blood culture are the tools available to investigate BA. Histopathologic study of skin or viscera confirms the diagnosis. With the biopsy sample, identification of the pathogen can be performed through culture as well as immunohistochemical and PCR techniques [86, 192]. Histopathology is typical, and shows lobular proliferation of small blood capillaries with large endothelial cells with abundant cytoplasm surrounded by inflammatory infiltrate, which contains many polymorphic nuclear leukocytes and focal necrosis. Optical microscopy provides visualization of *Bartonella* sp. through the Warthin–Starry stain [192].

Therapeutic Approach

All HIV-infected individuals diagnosed with *Bartonella* infection should receive antibiotic therapy. Drug options for cutaneous lesions include oral erythromycin (500 mg four times daily) and doxycycline (100 mg twice daily) for at least 3 months [166]. The intravenous route is appropriate for severe disease. Alternative agents include minocycline, azithromycin, clarithromycin, and ciprofloxacin [166].

Cutaneous Mycobacterial Infections

Mycobacterial infections with cutaneous manifestations are uncommon. Tuberculosis, hanseniasis, and, among the nontuberculous mycobacteria (NTM), the *Mycobacterium avium* complex (MAC), can affect the skin in HIV-infected patients. Treatment depends on the microorganism and the local resistance pattern.

General Epidemiology

Cutaneous manifestations associated with mycobacterial infections are uncommon. Although tuberculosis (TB) is the main opportunistic infection (OI) in HIV-infected individuals, cutaneous TB represents only 1–2% of TB cases [9, 209]. The cutaneous lesions caused by NTM, particularly the *M. avium* complex, are associated with advanced immunosuppression; especially with CD4 counts <50 cells/mm^3 [96].

Etiopathogenesis

The most relevant mycobacteria in the HIV-infected patient include *Mycobacterium tuberculosis* and *M. avium* complex [127]. Cutaneous infections by other mycobacteria, such as *Mycobacterium bovis*, *M. kansasii*, *M. marinum*, *M. malmoense*, *M. ulcerans*, *M. chelonae*, *M. fortuitum*, and *M. abscessus* are less common [96, 124, 209]. Depending on the epidemiologic characteristics of selected populations, some patients may acquire HIV–hanseniasis coinfection (*Mycobacterium leprae*).

Clinical Presentation

Cutaneous tuberculosis: the cutaneous tuberculosis presentation depends on the host immunologic status and environmental factors. The main clinical forms are verrucous tuberculosis, lupus vulgaris, miliary tuberculosis, and scrofuloderma (Dias et al. 2014; [96]). Scrofuloderma is the most common cutaneous form, occurring in skin by direct involvement from an underlying TB focus; and it is characterized by subcutaneous abscesses and nodules, with little inflammation and purulent secretion, mainly in the cervical, clavicular, and inguinal regions (Fig. 41.25). Lupus vulgaris may result from hematogenous dissemination of tuberculosis, or may occur at sites of inoculation or associated with scrofuloderma. The typical lesion is a raised plaque composed of red-brown papules, with "apple-jelly" aspect (Fig. 41.26).

Fig. 41.26 Cutaneous tuberculosis, lupus vulgaris: raised red-brown plaque with "jelly" aspect

Fig. 41.25 Cutaneous tuberculosis, scrofuloderma: subcutaneous abscesses and nodules, with little inflammation and purulent secretion; scarring of old lesions can also be seen

M. avium complex: its clinical presentation is variable and usually the cutaneous condition results from systemic infection. Papules, pustules, nodules, ulcers, abscesses, fistulas, and verrucous lesions may be the clinical expressions of the infection [96, 124].

M. leprae: clinical, immunologic, histopathologic, and virologic features among HIV/hanseniasis-coinfected patients indicate that each disease has progressed as in single infection. However, ART-induced immune reconstitution may trigger potential adverse effects, such as hanseniasis acute inflammatory episodes [9, 237].

Complementary Examinations

Diagnosis confirmation is based on histopathologic study and identification of *Mycobacterium* through PCR and/or culture. Samples can be obtained from a skin fragment or purulent discharge. Complementary diagnostic tools may be necessary for additional systemic investigation,

such as chest X-ray, sputum bacilloscopy, and Mantoux tuberculin skin test. QuantiFERON-TB Gold, a blood test that aids detection of *M. tuberculosis*, can be an auxiliary test, although it does not differentiate active from latent disease [96].

Therapeutic Approach

Treatment regimen depends on the isolated microorganism and the local resistance patterns. For cutaneous tuberculosis, the same therapy as for the pulmonary and extrapulmonary forms is used; in selected cases, a surgical approach may be necessary [124]. For disseminated MAC the optimal therapeutic regimen is not yet established. Treatment should include a minimum three-drug regimen of clarithromycin, rifampin, and ethambutol, until the patient is culture negative, after therapy for 1 year [120, 178]. Management of hanseniasis requires multidrug therapy recommended by the WHO and is covered in Chap. 6.

Fungal Infections

Candidiasis

Mucosal candidiasis has been associated with HIV disease from the initial description of early cases, and is the most common opportunistic fungal infection in HIV-positive patients. Oropharyngeal candidiasis is a marker for immunologic dysfunction and

is also a prognostic marker for the development of other subsequent OI in HIV-infected patients [255].

General Epidemiology

Candida species are ubiquitous fungi, and candidiasis is the most frequent fungal OI in association with HIV. Up to 90% of HIV-infected patients will develop oropharyngeal candidiasis at some stage of their disease [24]. Oral candida colonization occurs more frequently in HIV-positive patient in comparison with noninfected ones; it is significantly more common in patients with CD4 cell counts of <200 cells/mm^3, and a low CD4 count also seems to be associated with a higher density of yeast in the saliva of HIV patients [24, 188].

Etiopathogenesis

The genus *Candida* comprises yeast-like fungi that can form true hyphae and pseudohyphae. This genus consists of approximately 200 species, of which about 20 have been linked to human mycosis [57]. The species of clinical interest are *Candida albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, *C. krusei*, *C. guilliermondii*, and *C. lusitaniae*. However, several cases of superficial and invasive diseases and emerging species of *Candida* have been described [57, 230]. Less common species are more prevalent among HIV-infected patients, and some strains have showed decreased susceptibility to antifungal agents [206, 219]. Host defects play a significant role in the development of candidal infections. The intact skin constitutes a highly effective barrier to *Candida* penetration, and disruption of the skin allows invasion by colonizing opportunistic organisms. In addition, intravascular devices provide an efficient pathway that bypasses the skin barrier. The major defense mechanisms operating at the mucosal level to maintain colonization and prevent invasion include normal protective bacterial flora and cell-mediated immunity [291]. Candidiasis in HIV patients is strongly related to impaired anti-*Candida* defense mechanisms, both local and systemic, owing to the immunodeficiency [255].

Clinical Presentation

Candida infections can present in a wide spectrum of clinical syndromes, depending on the site of infection and the degree of immunosuppression of the host [291]. Oropharyngeal and esophageal candidiasis are the most common forms in HIV-infected patients, and *Candida* colonization of the oral cavity is a predisposing factor for the development of oral candidiasis in these patients [188]. The pseudomembranous is the most common form of oropharyngeal candidiasis and appears as white plaques, usually asymptomatic, on the buccal mucosa, palate, tongue, or oropharynx. The plaques can easily be rubbed off, a characteristic that distinguishes candidiasis from oral hairy leukoplakia, which presents fixed lesions. Less frequent forms of oral candidiasis are the acute atrophic stomatitis (midline glossitis), which refers to symmetric lesions on the dorsum of the tongue characterized by loss of papillae and erythema, and also the angular cheilitis (perlèche) that is characterized by soreness, erythema, and fissuring at the corners of the mouth [291]. The esophageal candidiasis is an AIDS-defining illness (CDC 1993), usually occurring at a much lower CD4 count and presenting with odynophagia or dysphagia. Candidal intertrigo affects the flexural folds in groins, genitals, armpits, under breasts, and abdominal folds. The pruritic erythematous patches can be seen at moist intertriginous areas, surrounded by slight scales and/or tiny pustules (Fig. 41.27). Candidal balanitis can present as itchy white patches on the glans penis, and the infection can also spread to the perigenital areas. Features of *Candida* vulvovaginitis, are nonmalodorous whitish vaginal discharge, pruritus, dysuria, and dyspareunia [218]. *Candida* vulvovaginitis, even if more frequent in HIV-infected

Fig. 41.27 Candidal intertrigo: pruritic erythematous patches in moist flexural folds

women, is clinically similar to that in HIV-negative women and does not appear to be of increased clinical severity [290]. *Candida* are true opportunistic pathogens that can gain access to the vascular circulation and deep tissues through technological devices (e.g., indwelling catheters) affecting high-risk patients who are either immunocompromised or critically ill and causing hematogenous dissemination of the yeast and disseminated candidiasis [291]. Cutaneous features are polymorphic in disseminated candidiasis and include erythematous macules, papules, pustules, and hemorrhagic or ulcerative lesions, or even abscesses.

Complementary Examinations

Typical aspects of most superficial *Candida* infections are quite characteristic to suggest the clinical diagnosis. Diagnosis is confirmed trough the visualization of budding yeast, with or without pseudohyphae, under microscopic examination of scrapings and smears, the addition of potassium hydroxide (KOH) 20%, or Gram stain.

Yeast culture is not usually performed, except for the resistant and recurrent cases. Although other forms of candidiasis should alert the physician to the possibility of underlying HIV infection, thus prompting them for HIV testing, routine screening for HIV is not recommended for women with vulvovaginal candidiasis unless other risk factors are present [292].

Therapeutic Approach

Treatment of candidiasis is variable and depends on the anatomic location of the infection, the patient's immune status, and risk factors for infection; and, in some cases, the *Candida* species as well as the susceptibility of the strain to antifungal drugs (Table 41.8) [291]. Detailed information regarding to the management of *Candida* infections can be found in specific and updated guidelines [57, 230]. Mild forms of candidiasis can be managed with local therapy. Cutaneous candidiasis can be treated with topical antifungal

Table 41.8 Treatment of candidiasis in HIV/AIDS patients

Candidiasis	Drug	Regimen
Cutaneous, mild	Topical antifungal agents[a]	Once or twice per day for 2 weeks or until clearance
Oropharyngeal, mild	Topical GV solution	0.00165%, bid for 7–14 days
	Nystatin suspension	100,000 U/mL, 4–6 mL, 4 times daily, for 7–14 days (swish for at least 2 min and swallow)
	Clotrimazole	One 10-mg troche 5 times daily, for 7–14 days
Moderate to severe; recurrent candidiasis; CD4 count <100/mm³	Fluconazole[b]	200 mg PO on first day, then 100–200 mg daily for 7–14 days
Esophageal	Fluconazole[b]	200–400 mg (3–6 mg/kg) PO daily for 14–21 days
		OR
		IV, 400 mg (6 mg/kg) daily; consider de-escalating to oral therapy as above once the patient is able to tolerate oral intake
VVGC, uncomplicated	Topical antifungal agents **OR**	Nystatin, daily, for 10–14 days **OR**
		Azoles, daily, for 3–5 days
	Fluconazole[b]	150 mg PO single dose
VVGC, compromised host	Fluconazole[b]	150 mg, PO two to three sequential doses 72 h apart
VVGC, recurrent	Induction therapy	Topical Azoles, daily, for 7–14 days **OR**
		Fluconazole 150 mg, PO 2 to 3 sequential doses, 72 h apart
	Maintenance therapy	Fluconazole 150 mg PO weekly for 6 months
VVGC, pregnancy	Clotrimazole or miconazole	Topical, daily for 7 days

Colombo et al. [57], Mukherjee et al. [201], Pappas et al. [230], Sobel [291, 292]
bid twice daily, *GV* gentian violet, *IV* intravenous, *PO* orally, *VVGC* vulvovaginal candidiasis
[a]Azoles, allylamines, butenafine, ciclopirox, and nystatin (no one agent superior to another) [230]
[b]Pregnancy: azoles should not be used during the first trimester

agents such asazoles, allylamines, butenafine, ciclopirox, and nystatin. The Cochrane HIV/AIDS Group evaluated the effects of interventions in treating oral candidiasis in children and adults with HIV infection. The study found no difference with regard to clinical cure between fluconazole and ketoconazole, itraconazole, and clotrimazole. Fluconazole, gentian violet, and ketoconazole were superior to nystatin. Continuous fluconazole was better than intermittent treatment [241]. Gentian violet solution at the concentration of 0.00165% does not stain the oral mucosa, is stable, and possesses potent antifungal activity; additionally it is an affordable option for the treatment of oropharyngeal candidiasis in HIV-infected patients in resource-limited settings [133, 201]. Vulvovaginal candidiasis in HIV-positive women can be treated by conventional methods including the use of maintenance suppressive antifungal therapy [292]. Systemic therapy with fluconazole is recommended for moderate to severe candidiasis, recurrent disease, and for immunosuppressed patients, because of the risk of esophageal candidiasis. In HIV-infected patients, ART appears to reduce the incidence of recurrent oral *Candida* infections and also to protect against vaginal colonization and candidal vulvovaginitis [4, 188, 230].

Dermatophytosis

Dermatophytosis (*tinea*) is a superficial infection caused by dermatophytes, fungi with great affinity to keratin, which proliferates in tissues such as skin, hair, and nails. In HIV-infected patients, immunosuppression may favor frequent exacerbations of dermatophytosis.

General Epidemiology

Dermatophytes are found universally; however, their relative prevalence may vary in different geographic areas according to climatic conditions or host lifestyles ([117]; Segal 2015). Dermatophytes can be transmitted via direct or indirect contact and there are three attributed sources of infection: humans (anthropophilic fungi); animals (zoophilic fungi), and soil (geophilic fungi). Population mobility, changes in human lifestyle, population aging, and use of antifungal drugs have been responsible for the continuous change in the epidemiology of dermatophytes [211, 277]. The anthropophilic dermatophyte *Trichophyton rubrum* is the most common etiologic agent in dermatophytosis worldwide [211, 277] as well as among HIV-infected patients [60, 138, 258, 284].

Etiopathogenesis

The etiologic agents of dermatophytosis are filamentous fungi in the genera *Microsporum*, *Trichophyton*, and *Epidermophyton* [117, 211]. Keratinolytic enzymes are important virulence factors of some dermatophytes, which possess the ability to utilize keratin from human and animal tissues, or debris from dead animals found in soil [211, 277]. The three genera can infect humans, causing dermatophytosis involving skin, hair, and nails [277]. The term onychomycosis means a fungal nail infection caused by dermatophytes, yeasts, or molds (or a combination of them), whereas tinea unguium refers to onychomycosis caused by a dermatophyte [212]. Predisposing host factors such as disorders of cellular immunity and genetic predisposition, among other factors, play a role in the development of dermatophytosis, especially onychomycosis [211]. The host response to cutaneous fungal infection may be abnormal in patients with HIV. Although dermatophytosis is common in HIV-positive and AIDS patients, the degree of immunosuppression does not seems to correlate with increased risk of this fungal infection [258, 284].

Clinical Presentation

Dermatophyte infections lead to a variety of clinical manifestations: tinea corporis (infection of body surfaces other than the feet, groin, face, scalp hair, or beard hair); tinea manuum (infection of the hands, Fig. 41.28); tinea pedis (infection of the foot, Fig. 41.29); tinea cruris (infection of the groin); tinea capitis (infection of scalp hair); and tinea unguium or dermatophyte onychomycosis (infection of the nail, Figs. 41.29 and 41.30) [212]. Tinea often begins
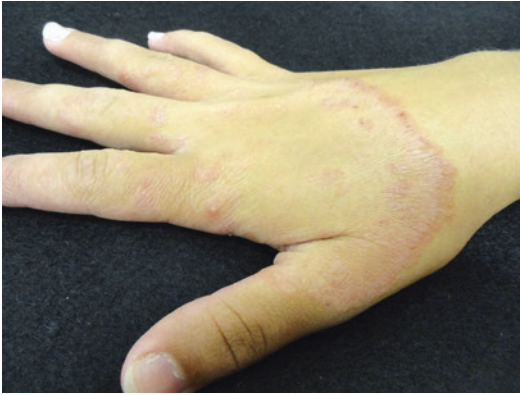
Fig. 41.28 Tinea manuum: erythematous plaque with well-defined edge with scale in the hand

Fig. 41.29 Tinea pedis and tinea unguium: chronic dry, scaling lesions in a "moccasin pattern" on the foot; the patient also has a dermatophyte onychomycosis with nail dystrophy of all toenails

Fig. 41.30 Tinea unguium: dermatophyte onychomycosis affecting all fingernails

Fig. 41.31 Tinea corporis: multiple erythematous scaling plaques with an annular configuration

as a pruritic, circular, erythematous, scaly patch that spreads centrifugally. Central clearing coexists with an active border, resulting in the characteristic annular shape of tinea corporis (Fig. 41.31). Multiple plaques may coalesce and vesicles occasionally appear. Tinea pedis has three major clinical types: interdigital, hyperkeratotic ("moccasin-type," Fig. 41.29), and inflammatory vesiculobullous. The most common clinical manifestation of tinea capitis, which almost always occurs in small children, is that of scaly patches with alopecia. Although rare cases of tinea capitis have been reported in HIV-infected adults [163, 207], children with AIDS are the most common cases and can present with severe tinea capitis (Fig. 41.32). Majocchi's granuloma is an example of dermal fungal involvement and is characterized by firm, violet-colored nodules and papules associated to onychomycosis, tinea corporis, or tinea pedis. Majocchi's granuloma may be precipitated by trauma to the skin or follicular occlusion; and

Fig. 41.32 Tinea capitis: scaly patches with alopecia in a severely ill HIV-infected child

Fig. 41.33 Tinea corporis: anergic form with extensive scaling lesions in an immunosuppressed HIV-infected patient

may also be favored by the immune dysfunction in immunosuppressed HIV patients [249]. There are several clinical subtypes of onychomycosis, and immunosuppressed patients with tinea unguium usually show involvement of multiple nails and total dystrophic onychomycosis (Figs. 41.29 and 41.30) ([60]; Surjushe et al. 2007). Dermatophytosis in HIV-infected patients can occur at some point during their illness; and tinea unguium and tinea pedis are the main clinical forms among HIV-infected patients [138, 258, 284]. Introduction of ART and prophylaxis with fluconazole for invasive fungal infection has reduced the incidence of dermatophytosis in HIV-positive individuals. However, dermatophytosis in these patients seems to present more frequently with atypical, multiple, extensive lesions and with little inflammation, called anergic forms (Fig. 41.33) [60, 132].

Complementary Examinations

The diagnosis of a cutaneous dermatophyte infection may be suspected based on the clinical findings. Nevertheless, atypical forms of *tinea* and onychomycosis should be confirmed by mycologic examination. Direct microscopic examination using KOH 20% aids in visualizing hyphae and spores, and confirming the diagnosis of dermatophyte infection [244]. A fungal culture allows the identification of dermatophyte species, and is useful when long-term oral therapy is being considered [113]. Though rarely used, DNA-based methods are effective for identifying mixed infections and quantification of fungal load.

Therapeutic Approach

Most dermatophyte infections can be managed with topical treatments. Effective topical antifungal agents include azoles, allylamines, ciclopirox, butenafine, tolnaftate, and amorolfine [71, 113, 139]. A meta-analysis evaluated the efficacy of antifungal treatment in the context of mycologic cure at the end of treatment and sustained cure. There were no statistically significant differences

among the antifungals concerning the outcome of mycologic cure at the end of treatment. For sustained cure, butenafine and terbinafine were each found to be superior to clotrimazole, although the difference in efficacy was not significantly large between antifungal classes [266].

Oral antifungal therapy is the option for some forms of tinea, for extensive infections, or infections refractory to topical therapy (Box 41.7) [269]. Terbinafine and itraconazole are the preferred systemic agents; griseofulvin and fluconazole can also be effective, but may require longer-term therapy (Gupta 2008; [139, 269]). Table 41.9 shows therapeutic options and regimens for dermatophytosis. According to the Cochrane Skin Group, oral treatments including terbinafine, itraconazole, and fluconazole are at least similar to griseofulvin in children with tinea capitis caused by *Trichophyton* species; the evidence also suggests that terbinafine is more effective than griseofulvin in children with *Trichophyton surans* infection, whereas in children with *Microsporum* infections the effect of griseofulvin is better than terbinafine [48]. For tinea unguium, treatment options include topical and systemic antifungal drugs. Clinical subtype, causative organism, disease severity, treatment side effects, and cost may influence the choice of therapy. Advantages of topical

> **Box 41.7 Systemic Antifungals: Indications for Dermatophytosis**
> - Tinea capitis
> - Tinea unguium
> - Tinea involving more than one body region simultaneously (e.g., tinea cruris and corporis, or tinea cruris and tinea pedis)
> - Extensive tinea corporis
> - Tinea pedis with extensive involvement of the sole, heel, or dorsum of the foot or when there is recurring and troublesome blistering
> - Patients who fail topical therapy
>   Sahoo and Mahajan [269]

Table 41.9 Treatment of dermatophytosis

Disease	Drug/regimen	
Limited tinea pedis, corporis, or cruris	Topical antifungal agents[d]	Once or twice per day for 4 weeks or until clearance
Tinea corporis and cruris	Systemic antifungals[e]	Terbinafine 250 mg daily; 3-6 mg/kg/day, for 2–3 weeks
		Itraconazole 200 mg daily, for 1–2 weeks
		Fluconazole 150–300 mg once weekly, for 3–4 weeks
		Griseofulvin microsize 500–1000 mg daily **OR**
		Griseofulvin ultramicrosize 300–375 mg daily, for 2–4 weeks
Tinea pedis	Systemic antifungals[e]	Terbinafine: 250 mg daily, for 2 weeks
		Itraconazole: 200 mg twice daily, for 1 week **OR**
		Itraconazole: 100–200 mg daily, for 2–4 weeks
		Fluconazole: 150 mg once weekly, for 4 weeks
		Griseofulvin microsize 750–1000 mg daily **OR**
		Griseofulvin ultramicrosize 660 or 750 mg per day for 4–8 weeks
Tinea capitis (regimen for children)[a]	Systemic antifungals[e]	Griseofulvin microsize 20–25 mg/kg/day, for 6 to 12 weeks; maximum 1000 mg per day
		Griseofulvin ultramicrosize 10–15 mg/kg/day, for 6–12 weeks; maximum 750 mg per day
		Terbinafine:
		10 to 20 kg: 62.5 mg daily, for 4–6 weeks
		20 to 40 kg: 125 mg daily, for 4–6 weeks
		Above 40 kg: 250 mg daily, for 4–6 weeks
		Fluconazole: 6 mg/kg/day, for 3 weeks **OR** 6–8 mg/kg/week. for 8–12 weeks
		Itraconazole: 5 mg/kg/day, for 2–4 weeks

Table 41.9 (continued)

Disease	Drug/regimen	
Majocchi's granuloma	Systemic antifungals[e]	Terbinafine 250 mg daily, for 2–4 weeks
		Itraconazole 200 mg twice daily for 1 week per month for 2 months
		Griseofulvin and daily itraconazole may also be used
Mild to moderate dermatophyte onychomycosis[b]	Topical antifungals	Efinaconazole 10% solution applied to the nails once daily for 12 months
		Amorolfine 5% nail lacquer once-weekly; fingernails for 6 months; toenails for 12 months
		Ciclopirox 8% nail lacquer applied to the nails once daily until nail clearance or up to 12 months
Moderate to severe dermatophyte onychomycosis[c]	Systemic antifungals[e]	Terbinafine 250 mg per day; fingernails for 6 weeks; toenails for 12 weeks
		Itraconazole pulse therapy: 200 mg twice daily for 1 week per month; fingernail for 2 months; toenail onychomycosis for 3 months
		Itraconazole continuous therapy: 200 mg per day; fingernail for 6 weeks; toenail onychomycosis for 12 weeks
		Fluconazole, 150–300 mg once weekly, for 6–12 months or longer[f]

Dias et al. [70, 71], Gupta and Cooper [109], Kelly [139], Piraccini and Alessandrini [244], Sahoo and Mahajan [269], Singal and Khanna [285], Welsh et al. [314]

[a]Fluconazole and itraconazole: alternative therapies, limited efficacy data for tinea capitis

[b]Distal lateral subungual onychomycosis involving ≤50% of the nail and sparing the matrix/lunula

[c]Involvement of >50% of the nail or of the matrix or lunula, proximal subungual or total dystrophic onychomycosis

[d]Azoles, allylamines, ciclopirox, butenafine, tolnaftate, amorolfine

[e]Pregnancy: oral azoles should not be used during the first trimester

[f]Not as effective or as cost-effective as itraconazole and terbinafine

therapy are the minor risk for drug interactions and adverse effects. However, topical antifungals have a limited efficacy if used without nail-plate debridement. A combination of both oral and systemic treatment is often the best choice [244]. Although initial therapy may result in complete or mycologic cure, relapse rates for onychomycosis remain high [109]. Box 41.8 displays topical monotherapy indications for onychomycosis [285].

> **Box 41.8 Topical Monotherapy Indications for Onychomycosis**
> - Involvement limited to distal 50% of nail plate, three or four nails involvement.
> - No matrix area involvement.
> - Superficial white onychomycosis (SWO).
> - In children with thin, fast growing nails.
> - Prophylaxis in patients at risk of recurrence.
> - Patients for whom oral therapy is inappropriate.
>   Singal and Khanna [285]

Periodic mechanical removal of the affected nail plate is recommended during the treatment. A nail clipper can be used for remove onycholysis. When several nails are involved and/or there is a lot of thickening, referral to an experienced podiatrist is advisable in order to avoid local injuries [314]. There is no specific guideline available for managing dermatophytic infection in HIV-infected patients and treatment should be individualized and based upon risk-benefit ratio. Due to possible associated comorbidities and drug interactions with several antiretroviral drugs the choice of systemic oral antifungal agent should be cautiously evaluated in HIV patients. Terbinafine clearance is significantly reduced in patients with renal failure and itraconazole should be avoided in hepatic impairment. In comparison with nontreated HIV patients, those under effective ART tend to have less frequent dermatophyte epidermal and nail infections, have infections that clear without specific antifungal therapy, respond better to antifungal therapy, and experience fewer recurrences [132].

Cryptococcosis

Cryptococcosis is an infectious disease with worldwide distribution and a wide array of clinical presentations caused by pathogenic encapsulated yeasts in the genus *Cryptococcus* [184]. Cryptococcal infections are extremely rare in people who are otherwise healthy; most cases occur in immunosuppressed patients, particularly those who have advanced HIV/AIDS.

General Epidemiology

Given the distribution of infections there are differences in the ecology of *Cryptococcus* species. *Cryptococcus neoformans* has been found worldwide, while *Cryptococcus gattii* is endemic in tropical and subtropical areas [45]. HIV infection is the major underlying condition predisposing to the development of cryptococcosis, which presents as a disseminated disease, usually when the CD4 count is <100 cells/mm^3 [11]. Up to 10% of HIV-seropositive individuals with disseminated cryptococcosis develop mucocutaneous lesions [45]. The extrapulmonary cryptococcosis is an AIDS-defining illness (CDC 1993).

Etiopathogenesis

Cryptococcus is a genus of basidiomycetous fungi containing more than 30 species. However, the common pathogenic organisms of cryptococcosis currently consist of two species with a predilection for the respiratory and nervous system of humans and animals. The two species, *C. neoformans* and *C. gattii*, are distinguishable biochemically and by molecular techniques, and there are also important species- and strain-specific differences with respect to geographic distribution, environmental niches, host predilection, and clinical manifestations [184]. Cryptococcosis is acquired through inhalation of basidiospores or desiccated yeast cells from the environment, and rarely by cutaneous route. The infection may be cleared, become latent, cause pulmonary infection, or disseminate, typically to the CNS. The factors that determine whether an exposed person develops symptomatic infection are uncertain but may include the inoculum of fungi (e.g., burden of exposure), virulence factors of the infecting strain, and impairment of cellular immunity [257].

Clinical Presentation

Cryptococcal infection is primary pulmonary, although in immune impaired hosts it can cause systemic illness, mainly affecting the CNS. Cutaneous infections are the third most common clinical manifestations of cryptococcosis [45]. The involvement of the skin is mostly secondary to hematogenous dissemination of the fungus and may act as a marker for disseminated infection, especially in patients with impaired cell-mediated immunity, such as HIV-infected patients. In disseminated cutaneous cryptococcosis the skin lesions can anticipate systemic signs of cryptococcosis and include the typical "molluscum-like" lesions (papules with central ulceration), nodules, abscesses, cellulitis, draining sinuses, ulcers, acneiform lesions, and vasculitic lesions, among others [45, 142, 205, 247]. Primary cutaneous cryptococcosis (PCC) is a distinct epidemiologic and clinical entity with a favorable prognosis even for immunocompromised hosts [213]. Most PCC is associated with local trauma and direct inoculation, and its dermatologic manifestations, usually confined to one body region, are protean and might mimic other cutaneous diseases: a single lesion at the site of infection, solitary nodule, plaque, ulcer, cellulitis, abscesses, and a sporotrichoid pattern have been described [45, 130, 213, 214]. In the case series published by Marques et al., PCC lesions presented more frequently as an infiltrative plaque or tumoral mass with a gelatinous consistency [172]. Cryptococcosis may also occur during IRIS in HIV-infected patients [112].

Complementary Examinations

Definitive diagnosis of cryptococcosis is made by isolation of *Cryptococcus* from a clinical specimen or direct detection of the fungus by means of India ink staining of body fluids [11]. The fungus can be cultured from biological samples such as CSF, sputum, and skin biopsy on routine fungal culture media [184]. *Cryptococcus* can be identified by histologic staining of skin and other tissues. The yeast is best identified by special stains that label the polysaccharide capsule including mucicarmine, periodic acid-Schiff (PAS), and Alcian blue stains [184]. Serologic

tests for detection of the cryptococcal polysaccharide capsular antigen can be performed with both serum and CSF using latex agglutination and enzyme immunoassay techniques, whose overall sensitivity and specificity are 93%–100% and 93%–98%, respectively [184].

Therapeutic Approach

Treating disseminated cryptococcosis consists of three phases: induction, consolidation, and maintenance therapy [236]. Table 41.12 shows recommended regimens by the WHO and by the United States Panel on OI in HIV infection [227, 228, 320]. The optimal antifungal regimen for non-

meningeal, nonpulmonary cryptococcosis has not been determined. In general, the suggested therapy is based on extrapolation from literature describing management of immunocompromised patients with mild to moderate pulmonary cryptococcosis in the absence of disseminated infection. Two recommended regimens are displayed in Table 41.10 [227, 228, 320]. Azole antifungals should be avoided during the first trimester of pregnancy. In HIV-infected patients with successfully treated cryptococcal disease, discontinuation of antifungal maintenance treatment is recommended when patients are stable and adherent to ART and antifungal maintenance treatment

Table 41.10 Treatment of cryptococcosis in HIV/AIDS patients

Drug	Regimen	Duration
Disseminated disease (Panel on OI in HIV recommendation)		
Induction therapy		
Liposomal amphotericin B[a] *plus*	3–4 mg/kg daily, IV	For 2 weeks
Flucytosine[a] **OR**	100 mg/kg PO daily in 4 divided doses	
Amphotericin B deoxycholate[a] *plus*	0.7-1 mg/kg daily, IV	For 2 weeks
Flucytosine[a] **OR**	100 mg/kg PO daily in 4 divided doses	
Amphotericin B (either liposomal or deoxycholate) *plus*	As above	For 2 weeks
Fluconazole[b] **OR**	800 mg PO daily	
Fluconazole[b] *plus*	400–800 mg daily	For 2 weeks
Flucytosine[a]	100 mg/kg PO daily in 4 divided doses	
Consolidation therapy		
Fluconazole[b]	400 mg PO daily	For 8 weeks
Maintenance therapy[c]		
Fluconazole[b]	200 mg PO daily	For at least 12 months
Alternative drug: Itraconazole[b,d]	200 mg PO daily	For at least 12 months
Disseminated disease (WHO recommendation)		
Induction therapy (for 2 weeks)	*Consolidation therapy* (for 8 weeks)	
Amphotericin B deoxycholate[a] 0.7–1 mg/kg daily, *plus* flucytosine[a] 100 mg/kg daily in 4 divided doses **OR**	Fluconazole[b] 400–800 mg daily	
Amphotericin B deoxycholate[a] 0.7–1 mg/kg daily, *plus* fluconazole[b] 800 mg daily **OR**		
Amphotericin B deoxycholate[a] 0.7–1 mg/kg/day short course (5–7 days), *plus* fluconazole[b] 800 mg daily for 2 weeks **OR**	Fluconazole[b] 800 mg daily	
Fluconazole[b] 1200 mg/day *plus* flucytosine 100 mg/kg/day **OR**		
Fluconazole[b] 1200 mg/day alone		
Maintenance therapy[d]		
Fluconazole[b] 200 mg daily, for at least 12 months		

Table 41.10 (continued)

Drug	Regimen	Duration
Localized nonmeningeal disease		
WHO recommendation	Panel on OI in HIV recommendation	
Induction therapy	Fluconazole[b] 400 mg daily, for 12 months	
Fluconazole[b] 800 mg daily, for 2 weeks (or 12 mg/kg/day up to 800 mg/day if <19 years)		
Consolidation therapy		
Fluconazole[b] 400 mg daily, for 8 weeks (or 6 mg/kg/day up to 400–800 mg/day if <19 years)		
Maintenance therapy[c]		
Fluconazole[b] 200 mg daily, for at least 12 months		

Panel on Opportunistic Infections in HIV [227, 228] and WHO [320]

Recommendations are listed in decreasing order of preference

Consider to delay initiation of ART by 2–4 weeks after starting antifungal therapy

Route of administration: amphotericin B (IV); flucytosine (oral); fluconazole (oral and IV)

ART antiretroviral therapy, *IV* intravenous, *OI* opportunistic infection, *PO* orally

[a]Monitor renal function

[b]Azole antifungals should be avoided during the first trimester of pregnancy

[c]Efficacy inferior to fluconazole

[d]Lifelong maintenance therapy in patients who do not attain immune recovery under ART

for at least 1 year, and have a CD4 cell count of ≥200 cells/mm³ (two measurements 6 months apart), or else when patient has a CD4 cell count ≥100 cells/mm³ (two measurements 6 months apart) and a suppressed viral load for at least 3 months [227, 228, 320]. The optimal time to begin ART and antifungal therapy is not established for forms other than cryptococcal meningitis; considering the risk of IRIS it would seem judicious to delay initiation of ART by 2–4 weeks after starting antifungal therapy [227, 228].

Histoplasmosis

Histoplasmosis, a systemic fungal infection caused by *Histoplasma capsulatum*, is the most common endemic mycosis in AIDS patients. The risk of disease in some HIV-infected populations has declined with effective ART; however, it still causes severe morbidity and mortality in resource-limited settings of endemic areas [210].

General Epidemiology

Histoplasmosis is mainly found in temperate zones worldwide and is more prevalent in certain regions of America, Africa, and Asia. In highly endemic areas, up to 20% of HIV-infected persons will develop disseminated histoplasmosis

[177]. Owing to the increase in travel and immigration, histoplasmosis has also been diagnosed in nonendemic areas [1, 177, 215, 226]. The fungus inhabits acidic soils rich in organic matter, particularly with birds and bat excreta, and transmission occurs via inhalation of fungal spores from the soil [317]. Histoplasmosis is considered as an AIDS-defining illness (CDC 1992) [39].

Etiopathogenesis

There are two identified species of dimorphic fungus associated with histoplasmosis: *H. capsulatum* var. *capsulatum*, which is the classic and HIV-associated histoplasmosis agent, and *H. capsulatum* var. *duboisii*, which causes African histoplasmosis [317]. The infection is primarily acquired via inhalation of fungal spores present in nature, which is followed by conversion into the yeast (pathogenic) fungal form at human body temperature [317]. The infection primarily affects the lungs causing localized pneumonitis, followed by hematogenous spread and cell-mediated immune response. Spontaneous resolution usually occurs in 95% of the patients, while in AIDS patients the infection can progress or become reactivated when CD4 levels decrease [257].

Clinical Presentation

Infection may range from asymptomatic presentation to disseminated disease, the latter affecting mostly immunocompromised individuals, particularly those infected with HIV [123]. AIDS patients usually develop progressive disseminated histoplasmosis, a febrile, wasting illness [17]. Mucocutaneous involvement is a common manifestation of disseminated histoplasmosis in HIV-infected patients with CD4 count of $<50/mm^3$. Skin and mucosal lesions can occur with a variable prevalence, uncommon in the United States (<10%), while representing 38–85% of reported AIDS cases in Latin America [62]. A wide spectrum of skin lesions is observed, including disseminated papules, plaques, and nodules with and without crusts, in a diffuse pattern of distribution (Fig. 41.34), more marked on the face. Morphologic variability of lesions seems to be associated with higher CD4 cell counts [62]. Other findings can be seen, such as macules, papulopustules, necrosis, and molluscum-like lesions (Fig. 41.35) [220]. Up to two-thirds of patients experience mucosal involvement, particularly in the oropharyngeal region [257]. Primary skin lesions are uncommon in histoplasmosis. As with other HIV-related systemic mycoses, skin manifestations can be part of histoplasmosis-related IRIS, after starting ART [34].

Fig. 41.34 Histoplasmosis: disseminated erythematous papules with central crusts

Fig. 41.35 Histoplasmosis: molluscum-like papules on the face

Complementary Examinations

Laboratory observations used to support diagnosis of disseminated histoplasmosis include investigation of anemia, leukopenia, thrombocytopenia, abnormal liver enzymes, elevated lactate dehydrogenase, and ferritin [257]. There are multiple diagnostic tests for disseminated *H. capsulatum* infection, including culture, serology, antigen testing, and direct microscopy. Definitive diagnosis is based on histopathology and/or the isolation of *H. capsulatum* in culture of clinical specimens, such as cutaneous, respiratory, peripheral blood, and bone marrow samples [136]. Limitations of culture are its time-consuming character and the usually low sensitivity (<60–85%, depending on the fungal load, the type of sample, and laboratory skills) [123]. Antibody detection by immunodiffusion or complement fixation has low sensitivity (50–70%) in immunocompromised HIV-infected patients [317]. Enzyme immunoassay methods can detect *H. capsulatum* polysaccharide antigens on several samples (urine, serum, CSF, and bron-

choalveolar fluid) allowing for a rapid and noninvasive diagnosis [123]. A recent diagnostic meta-analysis on the performance of *Histoplasma* antigens has revealed a high specificity (98%) and sensitivity (81%) for antigen detection in both urine and serum [79]. A simple and less expensive test (not definitive) is the direct microscopy of skin lesions scrapings or body fluids, stained with Giemsa or PAS stain, in order to visualize budding yeasts. Although histopathologic study with specific stains is very helpful, culture is still the gold standard for diagnosis [257].

Therapeutic Approach

Since morbidity and mortality associated with disseminated histoplasmosis remains high in patients who are not under treatment for HIV infection, ART should be initiated as soon as possible to recover cellular immunity. Disseminated histoplasmosis in the HIV-infected host is fatal without therapy [316]. Management includes a phase of induction therapy, followed by long-term maintenance (Table 41.11). The treatment is chosen according to disease severity and immune status. Patients with severe immunosuppression,

Table 41.11 Treatment of histoplasmosis in HIV/AIDS patients

Moderately severe to severe disease	Mild disease
Induction therapy	*Induction and maintenance therapy*[a, b]
Liposomal amphotericin B, 3 mg/kg/day, IV, for 2 weeks or until clinically improved; **OR**	Itraconazole 200 mg PO tid for 3 days, followed by 200 mg bid for at least 12 months
Amphotericin B deoxycholate 0.7 mg/kg daily, IV, for 2 weeks or until clinically improved	
Maintenance therapy[a, b]	
Itraconazole 200 mg PO tid for 3 days, followed by 200 mg bid for at least 12 months	

Panel on Opportunistic Infections in HIV [227, 228], and Wheat et al. [316]
Initiate ART as soon as possible
ART antiretroviral therapy, *bid* two times daily, *tid* three times daily, *IV* intravenous
[a]Do not use alternative agents to itraconazole
[b]Lifelong maintenance therapy with itraconazole in patients who do not attain immune recovery on ART

disseminated disease, organ dysfunction, or pancytopenia are classified as having moderately severe to severe disease and require amphotericin B as the first-choice drug. Patients with mild disease and a single focus of histoplasmosis (other than CNS) have mild to moderate disease and can receive oral itraconazole. Suppressive therapy is mandatory in patients who continue to be immunosuppressed and itraconazole is the preferred oral azole. Monitoring of patients can be attained by checking antigen levels quarterly during therapy to assess treatment response [227, 228, 316]. Antigen monitoring during suppressive therapy is not routinely recommended.

Sporotrichosis

Sporotrichosis is a granulomatous subcutaneous mycosis that has a worldwide distribution and several clinical manifestations. It remains a relevant public health problem in endemic areas, affecting a large at-risk population, which includes HIV-infected individuals. HIV infection aggravates the course of sporotrichosis, leading to a higher incidence of severe disseminated cases and a higher number of hospitalizations and deaths [88, 97].

General Epidemiology

Sporotrichosis is an endemic disease prevalent worldwide in tropical and subtropical areas; and its ecology, epidemiology, and clinical features vary across different geographic regions [43, 250]. The mycosis has a high prevalence in Latin America, especially in Brazil, Peru, and Colombia, and is also endemic in India, China, Japan, and South Africa [5]. Infections are usually sporadic and caused by traumatic inoculation of decaying plant matter, hay, soil, and sphagnum moss, but outbreaks have been associated with traumatic skin injury or with zoonotic spread from infected animals, especially domestic cats [19, 102]. Sporotrichosis may be the initial presentation of HIV infection in 27% of cases [197], and the coinfection is associated with poor outcome [88, 197].

Etiopathogenesis

The *Sporothrix schenckii* complex members, which are dimorphic fungi, cause sporotrichosis.

The virulence-related phenotypes are variably expressed within the multiple cryptic species and might be involved in the wide spectrum of clinical aspects of the disease [5].

Clinical Presentation

A wide spectrum of clinical manifestations is observed in sporotrichosis, ranging from cutaneous, subcutaneous, and disseminated cutaneous forms to pulmonary or systemic presentations (Almeida-Paes 2015). Several factors may influence the clinical presentations of sporotrichosis: the immunologic status of the host, the load and depth of the inoculum, and the pathogenicity of the strain, among others [19]. In cutaneous forms, the infection usually appears after minor trauma. After penetrating through the skin, the fungus converts into the yeast form and may remain localized in the subcutaneous tissue [19]. The initial presentation of sporotrichosis is a papule at the site of injury, which becomes a nodule that usually ulcerates but may remain nodular with overlying erythema or erythematosquamous lesion, constituting the fixed form of sporotrichosis. Weeks after development of the primary lesion, similar lesions may subsequently occur along the lymphatic path proximal to the original lesion, a characteristic named "sporotrichoid" pattern or "ascending nodular lymphangitis" (Fig. 41.36). The lymphocutaneous form is the most frequent form of sporotrichosis. Osteoarticular and pulmonary involvement accounts for some of the extracutaneous forms [274]. Eventually, the fungi may spread through hematogenous route, characterizing the disseminated cutaneous form, which typically presents as subcutaneous nodules and has mainly been observed among immunosuppressed patients, especially HIV-infected individuals. On rare occasions, inhalation of conidia may lead to a systemic disease. Disseminated cutaneous forms have been observed among immunosuppressed patients, especially HIV-infected individuals [88]. A recent systematic review on published data of HIV-associated sporotrichosis, performed by Moreira et al., found a low median CD4 count (97 cells/mm^3) and 30% mortality rate among 58 patients [197]. Although the skin is the most commonly affected organ, multiorgan dissemination is more frequent in the coinfection, probably due to underlying HIV-related immunosuppression; additionally, a tropism for the CNS occurs

Fig. 41.36 Lymphocutaneous sporotrichosis. Nodules (**a**) and nodulo-ulcerative lesions (**b**) along lymphatic path proximal to the original lesion ("sporotrichoid" pattern or "ascending nodular lymphangitis") in the arm and forearm (Photograph **a** courtesy of Dr. Andre Avelino Costa Beber, Hospital Universitário de Santa Maria, Brazil)

and is almost always fatal [88, 197]. IRIS-associated sporotrichosis accounted for 7.5% of cases, and such AIDS-patients were severely immunosuppressed and had a high HIV viral load at baseline (pre-ART), showing new disease manifestations or reactivation of pre-existing lesions in a median time of 4 weeks after ART initiation [197]. Based on the characteristics of the coinfection sporotrichosis/HIV, some authors have considered *Sporothrix* spp. as an opportunistic pathogen and have suggested the inclusion of disseminated sporotrichosis as an AIDS-defining illness in endemic areas for this mycosis [88, 93, 197].

Complementary Examinations

Culture is the gold standard for establishing a diagnosis of sporotrichosis; it is the most sensitive method and samples include aspirated material from a lesion, tissue biopsy, sputum, or body fluids [19]. Laboratory tools for diagnosis of sporotrichosis also include direct and histopathologic examination aided by special stains. The histology shows a mixed suppurative and granu-lomatous inflammatory reaction in the dermis and subcutaneous tissue, frequently accompanied by microabscess and fibrosis. The organisms, with characteristic "cigar-shaped" buds, may eventually not be visualized even with special stains, such as Gomori methenamine silver and PAS, because of the paucity of yeasts in lesions [19]. Serology is not used routinely in the diagnosis of sporotrichosis.

Therapeutic Approach

The choice of antifungal drug in patients with sporotrichosis is limited, and Table 41.12 lists the available options and regimens. Itraconazole is currently the first-choice treatment for cutaneous and lymphocutaneous forms of sporotrichosis and as suppressive therapy in immunocompromised patients after induction with amphotericin B [19]. Amphotericin B is the preferred agent for initial treatment of disseminated forms, especially in immunocompromised individuals [135]. In the case series reported by Freitas et al., itraconazole was noted to be effective in several sporotrichosis/HIV-coinfected patients who had the

Table 41.12 Treatment of sporotrichosis

	Preferred treatment	Alternative treatment
Disseminated disease	Liposomal amphotericin 3–5 mg/kg/day IV, until improvement	Amphotericin B deoxycholate 0.7–1 mg/kg/day IV, until improvement
	Maintenance therapy[a]: itraconazole 200 mg PO bid, for a total of at least 12 months	
Cutaneous or lymphocutaneous	Itraconazole 200 mg PO daily	Itraconazole 200 mg PO bid[b]; **OR**
		Terbinafine 500 mg PO bid; **OR**
		SSKI PO with increasing doses; **OR**
		Fluconazole 400–800 mg/day PO; **OR**
		Local hyperthermia
	Maintenance therapy: treatment for 2–4 weeks after lesions have resolved	
Pregnant women	*Severe sporotrichosis*	When possible, defer treatment to post delivery
	Liposomal amphotericin 3–5 mg/kg/day IV; **OR** amphotericin B deoxycholate 0.7–1 mg/kg/day IV	
	Lymphocutaneous or cutaneous sporotrichosis	
	Local hyperthermia	
Children	*Severe sporotrichosis*	SSKI with increasing doses equivalent to half the adult dose
	Amphotericin B deoxycholate 0.7–1 mg/kg/day IV	
	Lymphocutaneous or cutaneous sporotrichosis	
	Itraconazole 6–10 mg/kg/day PO, until maximum of 400 mg/day	

Panel on Opportunistic Infections in HIV [227, 228], and Kauffman et al. [135]

Consider to delay initiation of ART by 2–4 weeks after starting antifungal therapy

ART antiretroviral therapy, *bid* twice daily, *IV* intravenous, *PO* orally, *SSKI* saturated solution potassium iodide

[a]Long-term maintenance therapy with itraconazole in patients who do not attain immune recovery on ART

[b]Dose of 400 mg/day PO should be administered for cutaneous forms with a poor initial response to a lower dosage

disseminated form [87]. Although the exact mechanism of action remains unknown, potassium iodide has been traditionally used in the treatment of sporotrichosis with satisfactory results (Casta et al. 2013; [248]). However, its efficacy is not established in immunosuppressed patients. In a saturated solution of potassium iodide (SSKI) one drop is equivalent to 50 mg of SSKI; the recommended dose in adults is 250 mg or five drops of SSKI, with increments of three drops (150 mg)/dose daily until a maximum dose of 30–40 drops (1.5–2.0 g) three times a day, or until the patient experiences unpleasant side effects. In children, the recommended dose is three drops three times a day, increasing by one drop per kilogram per dose to a maximum of 25 drops three times a day [248]. Treatment is limited by side effects including gastrointestinal disturbance, rash, salivary gland enlargement, metallic taste, and thyroid dysfunction [248]. Potassium iodide and itraconazole are contraindicated in pregnant women, and thermotherapy can be used for these patients, with daily application of local heat (42–43 °C) through a hot water bag, a source of infrared, or a similar method until healing of lesions [19, 135]. Sporotrichosis/HIV-coinfected patients should receive suppressive therapy with itraconazole until immune system recovery, and it seems reasonable to discontinue therapy for those who have been treated with itraconazole for at least 1 year and whose CD4 cell counts have remained >200 cells/mm^{3}for at least 1 year [135]. The impact of and the best time for ART initiation during sporotrichosis infection are unknown. Moreira et al. have pointed that ART should be delayed in high-risk patients (CNS disease, low CD4 cell count and high viral load) because of predisposition to IRIS-related meningeal sporotrichosis [197].

Ectoparasitic Infestations

Scabies

Scabies is an infestation of the skin caused by the mite *Sarcoptes scabiei* resulting in an intensely itchy rash with a characteristic distribution pattern.

General Epidemiology

The prevalence of scabies undergoes cyclical fluctuations on a worldwide basis. A recently published systematic review has found a wide range of scabies prevalence worldwide (North America data not available): from 0.2% to 71.4%. In all regions except for Europe and the Middle East the prevalence was greater than 10%. Overall, scabies prevalence was highest in the Pacific and Latin American regions [261]. Scabies affects individuals of different ages, races, and socioeconomic conditions. It is more prevalent in crowded conditions and is primarily transmitted through close personal contact, whereas fomite transmission may occur only rarely [66, 107].

Etiopathogenesis

Human scabies is caused by the mite *S. scabiei* var. *hominis*. The incubation period varies from days to months, and is about 3–6 weeks when the first infection occurs [107]. Pruritus and rash occur as the result of a delayed type-IV hypersensitivity reaction to mite proteins in mite saliva, feces, eggs, and the mite itself. For this reason, signs and symptoms of infestation, such as pruritus and rash, typically develop 3–4 weeks after primary exposure, or 1–2 days after re-exposure [66, 262].

Clinical Presentation

The main symptom of scabies is the intense pruritus, which is accentuated at night and after bathing [107]. The characteristic skin lesions are erythematous dome-shaped 2 - to 3-mm papules, linear excoriations, burrows, and eventually, nodules (Fig. 41.37). The pathognomonic finding is the burrow, a short erythematous pink or white linear papule, resulting from a female mite penetrating and burrowing into the skin (Fig. 41.37). Lesions are most frequently found in the finger webs or on flexor surfaces of the wrists, on the elbows, axillae, buttocks, areolae, and genitalia in adults (Fig. 41.38), or on the face, neck, hands, and feet in infants [107, 173]. Immunosuppressed patients may develop crusted scabies (CS), which is an atypical highly contagious disease caused by hyperinfestation [107]. The initial clinical picture of CS presents erythematous plaques that rapidly evolve to thick crusts, predominating in
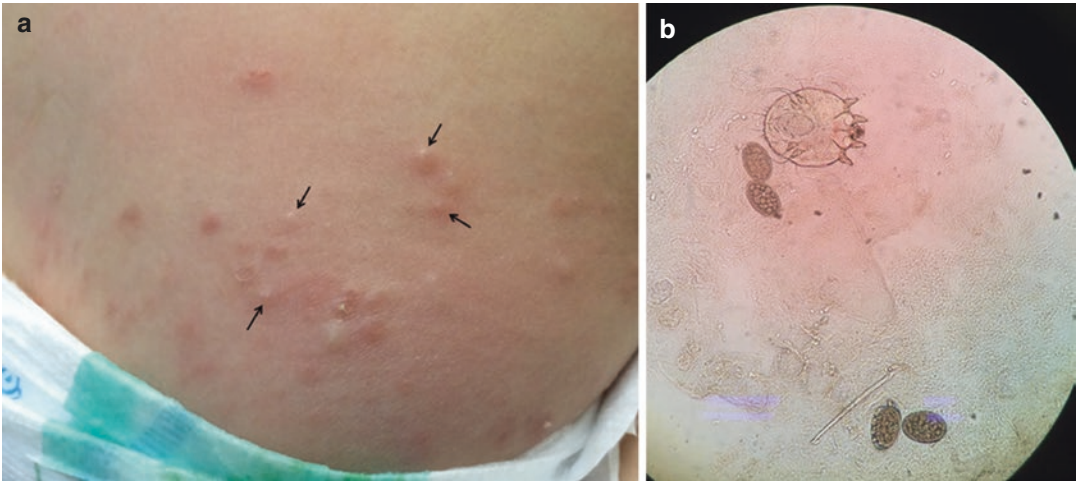
Fig. 41.37   Scabies: pruritic papules and burrows (*arrows*) (**a**); mite, ova, and feces (tiny black dots) (**b**)
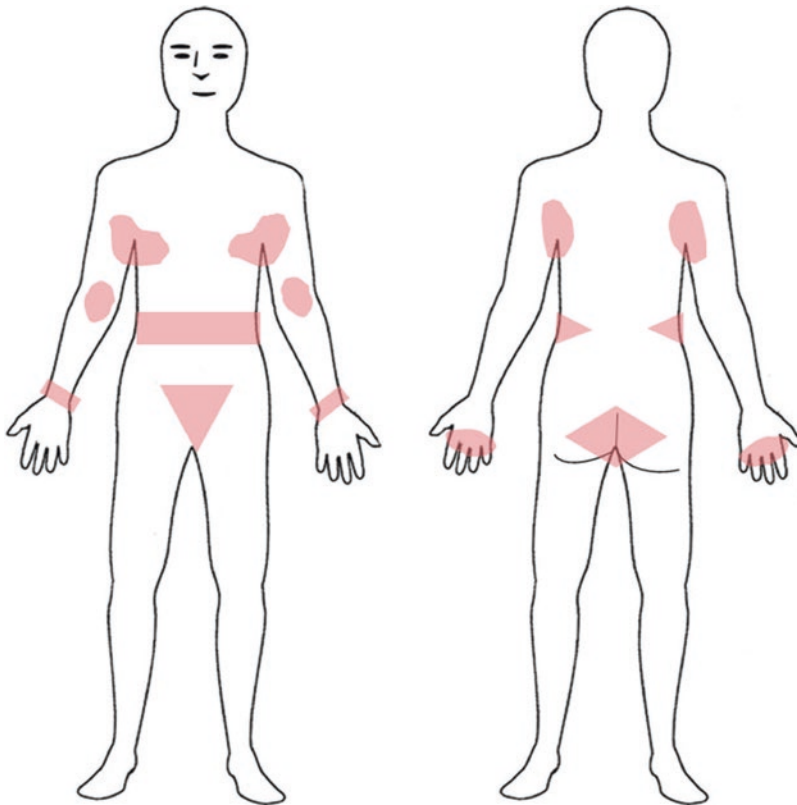
Fig. 41.38   Topography of scabies lesions in adults

the palmoplantar and subungual regions; generalized erythematous scaling eruptions (Fig. 41.39) and scalp involvement may spread leading to erythroderma. Pruritus is mild or absent in CS because of impairment of the host's immune response. The CS/HIV coinfection exhibits a chronic disease with a variable clinical picture; often with psoriasiform appearance and large

Fig. 41.39 Crusted scabies: disseminated rash (a); heavy scaling and crusts on the scalp (b) and finger webs (c)

numbers of mites in the lesions. Although CS is typically associated with immunosuppressed status, 80% of CS/HIV-coinfected patients reported by Tirado-Sanchez had a CD4 count >200 cells/mm^3 [301]. CS/HIV coinfection has also been described as part of the IRIS [82].

Complementary Examinations

The diagnosis is usually established by clinical history, added to the information of similar symptoms among close contacts, and clinical presentation. Dermoscopy can be useful in helping visualization, when a tiny black dot may be observed at one end of the burrow, which is the actual mite [103, 302]. Definitive diagnosis relies on microscopic identification of the mites, eggs, or fecal pellets from scrapings of the skin, which should be taken from nonexcoriated burrows, papules, or vesicles (Fig. 41.37) [262]. Skin biopsy may also be necessary in erythroderma or dubious cases.

Therapeutic Approach

Uncomplicated scabies/HIV-coinfected patients should receive the same treatment regimens as those who are HIV negative. Simultaneous treatment of the patient and close contacts is recommended. The first-line acaricide is topical permethrin 5%. Oral ivermectin is considered a second-line therapy option if treatment with topical permethrin is unsuccessful [107]. Women who are breastfeeding or pregnant and children who weigh less than 15 kg should not be treated with oral ivermectin. Topical permethrin 5% appears to be safe and effective for infants younger than 1 month of age. Cotton mitts or socks on the hands of infants and young children prevent them from rubbing the cream into their eyes and mouth. Topical application of 8–10% precipitated sulfur for 3 consecutive days, although messy and malodourous, is an effective alternative therapy still used because

Table 41.13 Therapies for scabies

	Classic scabies	Crusted scabies[a]
Topical therapy[b]		
Permethrin 5% cream, lotion	Two applications, 1 week apart; **OR** systemic therapy	Once daily for 7 days, then twice weekly until cure; *plus* systemic therapy
Alternative topical therapy		
8–10% precipitated sulfur in petrolatum	Three consecutive nights	
Systemic therapy		
Oral ivermectin	200 µg/kg/dose, two doses 1 week apart	200 µg/kg/dose on day 1, 2, 8, 9, and 15 (22 and 29 for severe infestations)

Mounsey and McCarthy (2013), and UK Scabies Guideline [304]
[a]Keratolytic creams should be used for skin crusts
[b]Apply thoroughly into the skin (except the face), including under the fingernails and toenails; maintain overnight or for 8 h, and washed off

of its low cost and its wide margin of safety in newborns, infants, and pregnant women [200]. Crusted scabies represents a treatment challenge. Dual therapy with oral ivermectin plus topical permethrin 5% is recommended for extended time (Mounsey and McCarthy 2013; [304]). Table 41.13 lists drugs and doses for the treatment of scabies. The pruritus may continue for up to 2 weeks after successful treatment. Oral antihistamines can help to control itching and, after eradication of mites, medium- or high-potency topical corticosteroids can be used (Mounsey and McCarthy 2013). Bedding, clothing, and towels used in the last week by infested persons or their household, sexual, and close contacts should be washed at high temperature (60 °C) and dried in a hot dryer, by dry-cleaning, or by sealing in a plastic bag for at least 72 h [304].

Demodicidosis

Demodex mites are the largest and most complex organisms of the skin microflora and are associated with cutaneous inflammatory disorders such as demodicidosis, also known as demodicosis.

General Epidemiology

It is estimated that 20% of general population harbors *Demodex* mites, while the prevalence in HIV-infected patients ranges from 20% to 95%, and there is a trend of increasing prevalence when the CD4 count falls [145, 325].

Etiopathogenesis

Demodicidosis is an infestation caused by the cutaneous saprophytic mites *Demodex folliculorum* and *Demodex brevis*, which are natural host of the human pilosebaceous follicle. A high concentration of *Demodex* is found in cutaneous areas with numerous sebaceous glands, and eyelashes are a common site of infestation [325]. Their potential to have a pathogenic role in the causation of human skin disorders is still unknown (Chen and Plewig 2014). Altered immune system and/or unusual hypersensitivity against the mite itself could favor the growth of these usually saprophytic agents, thus eventually causing demodicidosis [13, 149].

Clinical Presentation

Clinical presentation is heterogeneous and includes pruritic papules, vesicles, pustules, folliculitis and rosacea-like lesions, plaques, granulomatous and even cystic facial lesions (Chen and Plewig 2014). The rash may be itchy and may also be found on the chest and upper limbs. In HIV-infected patients most demodicidosis cases have occurred in association with CD4 counts of <200 cells/mm^3, and the majority of patients had a facial papulopustular-type rosacea clinical pattern (Fig. 41.40) [53, 326]. Crusted demodicidosis has been described in an HIV-infected female and also in an immunocompetent child, although the severe clinical manifestations in the latter patient could be attributed to local immunosuppression secondary to chronic use of topical steroids [36, 106].

Fig. 41.40 Demodicidosis: facial papulopustular-type rosacea clinical pattern

Complementary Examinations

The diagnosis of demodicidosis depends primarily on the clinical appearance of skin lesions and demonstration of mites on microscopic examination of scrapings (Fig. 41.41). Diagnosis can be made by standardized skin surface biopsy or skin scraping, usually considering abnormal anything more than five mites per cm^2 [46]. As the presence of *Demodex* mites in a specimen is not equivalent to a diagnosis of demodicosis, skin biopsy evaluated in the context of clinical history and appearance is important to confirm the diagnosis [268].

Therapeutic Approach

Treatment of human demodicosis is based on single case reports and is weakly evidence based [46]. Various treatments have been used for *Demodex*-associated skin eruptions, including topical permethrin 5% cream, topical sulfur, oral ivermectin, and oral metronidazole [77]. For mild demodicidosis topical permethrin 5% can be applied to the entire face and other affected areas at night and washed off after 8–14 h, for three consecutive nights on a weekly basis. In cases not responsive to topical

Fig. 41.41 *Demodex* mite (potassium hydroxide preparation of a skin scraping)

treatment, oral ivermectin can be given as two 200-μg/kg doses separated by 1 week. Another possible regimen is metronidazole 0.75% gel and/or oral metronidazole 250 mg three times daily for 3 weeks [125].

Protozoal Diseases

Tegumentary Leishmaniasis
The leishmaniases are among the neglected tropical diseases listed by the WHO. They are caused by species of protozoa of the genus *Leishmania* that are transmitted to humans by phlebotomine sandflies. HIV and *Leishmania* reinforce each other in a deleterious way. The *Leishmania* genus has multiple species that cause cutaneous, mucosal, and/or visceral disease.

General Epidemiology
Leishmaniases prevail in tropical and subtropical areas and in southern Europe, although socioeconomic factors, population mobility, and environmental and climate changes make them also prevalent in nonendemic areas [7, 319]. More than 90% of global visceral leishmaniasis cases occur in six countries: India, Bangladesh, Sudan, South Sudan, Ethiopia, and Brazil. Tegumentary leishmaniasis is more widely distributed, with about one-third of cases occurring in the Americas, the Mediterranean basin, and western Asia from the Middle East to Central Asia [324]. The complex biological system that favors leishmaniasis transmission involves the human host, parasite, sandfly vector, and sometimes an animal reservoir [319]. *Leishmania*/HIV coinfection is considered a serious emerging disease in several regions of the world. The urbanization of leishmaniases and the spread of HIV have led to a geographic overlap of these two infections, and epidemiologic projections estimate a continuous growth of the *Leishmania*/HIV coinfection [32, 319].

Etiopathogenesis
The leishmaniases are a group of noncontagious chronic infectious diseases resulting from macrophage parasitism by protozoan parasites belonging to the genus *Leishmania*, more than 20 species being known. The parasites are transmitted by insect vectors, the phlebotomine sandflies. The infection can result in cutaneous, mucous, and visceral diseases [114]. The genus *Leishmania* is divided into two subgenera: the subgenus *Leishmania* and the subgenus *Viannia*. Tegumentary leishmaniasis is caused by multiple species of both the *Leishmania* and *Viannia* subgenera [319]. The leishmaniases can also be classified according to the source of human infection: in zoonotic leishmaniases the reservoir hosts are wild animals, commensals, or domestic animals; and in anthroponotic leishmaniases the reservoir is human [319]. *Leishmania* and HIV may have enhanced reciprocal effects, especially in relation to the visceral leishmaniasis, as dual infection plays an important role in the pathogenesis, clinical latency, and disease progression of either infection. The immunologic deregulation caused by HIV favors the multiplication of the parasite in tegumentary forms of *Leishmania*/HIV coinfection [6].

Clinical Presentation
Leishmaniases comprise both visceral and tegumentary forms. While tegumentary leishmaniasis (TL) is the most frequent form of the disease, visceral leishmaniasis (VL, also known as kala-azar) is the most severe and life-threatening one [324]. Post-kala-azar dermal leishmaniasis (PKDL) is a cutaneous disease that occurs during or after visceral leishmaniasis associated with viscerotropic *Leishmania* species. TL comprises the cutaneous and mucocutaneous forms, which can be localized, disseminated, or diffuse in distribution and may differ in Old and New World regions (Goto and Lindoso 2012). Based on clinical presentations, cutaneous leishmaniases are classified as localized cutaneous leishmaniasis (LCL), diffuse cutaneous leishmaniasis (DCL), disseminated leishmaniasis, leishmaniasis recidiva cutis (LR), and mucosal leishmaniasis (ML) (Goto and Lindoso 2012). Although some clinical

manifestations are more frequently associated with a particular species or subgenus, none is unique to a species [319]. The clinical features of TL are diverse, depending on the *Leishmania* species and host immune response. However, the natural history of the primary lesion is similar. At the site of inoculation a macule appears, followed by a papule, then a nodule that ulcerates and expands to a typical round-to-oval craterform lesion, or evolves as a nodule. Lesions can develop weeks, months, or years after infection, but usually the incubation period ranges from 2 weeks to 3 months. Primary lesions may be single or multiple, and lymphatic involvement manifests as lymphadenitis or lymphadenopathy. The primary lesion may spontaneously heal or may persist as an ulcer, yet some lesions may then evolve into other chronic forms (Goto and Lindoso. 2012; [319]). The main clinical aspects of TL are briefly described in Box 41.9; detailed descriptions can be found in the WHO Report, Control of Leishmaniases [319]. *Leishmania*/HIV coinfection has changed the classical picture of visceral and other forms of the disease, since HIV and *Leishmania* reinforce each other in a deleterious manner. Immunosuppressed status may alter the clinical presentation and treatment response of leishmaniases. In *Leishmania*/HIV-coinfected patients, especially in patients with a low CD4 count (<200 cells/mm³), TL may show clinical variability, with atypical, multiple, polymorphic lesions and relapsing disease [105, 159, 307]. Cutaneous or mucocutaneous forms can be associated with VL, and visceralization of

DL: disseminated multiple pleomorphic lesions, in two or more noncontiguous areas of the body; acneiform papules; extensive nodular or ulcerated lesions; mucosal lesions are frequent (Fig. 41.43)

DCL: rare and true anergic form; multiple papules, nodules, or tubercles with diffuse cutaneous infiltration and no ulceration; usually no mucosal lesions; do not heal spontaneously; frequent relapses after treatment

ML/MCL: destructive lesions of mucosal tissues of the mouth and upper respiratory tract; occurs years after the onset of cutaneous leishmaniasis (Figs. 41.44 and 41.45)

PKDL[a]: cutaneous disease during or after visceral leishmaniasis associated to viscerotropic *Leishmania* species

TL/HIV: atypical manifestations; macules, nodules, crusted plaques, multiple exudative ulcers, including genitals; oral diffuse infiltration; diffuse cutaneous leishmaniasis with ulcers

Goto and Lindoso [100], Handler et al. [114], WHO [319]

DCL diffuse cutaneous leishmaniasis, *DL* disseminated leishmaniasis (cutaneous), *LCL* localized cutaneous leishmaniasis, *LR* leishmaniasis recidiva cutis, *ML/MCL* mucosal leishmaniasis/mucocutaneous leishmaniasis, *PKDL* post-kala-azar dermal leishmaniasis, *TL* tegumentary leishmaniasis, *TL/HIV* tegumentary leishmaniasis/HIV coinfection

[a]Not TL; it is instead visceral leishmaniasis with cutaneous lesions

Fig. 41.42 Localized cutaneous leishmaniasis, "classical form": painless, round-to-oval, craterform ulcer usually on an exposed skin area (Photograph courtesy of Dr. Ana Lucia França da Costa, Faculdade de Medicina da Universidade Federal do Piauí, Brazil)

Box 41.9 Clinical Forms of Tegumentary Leishmaniasis

LCL: "classical form"; painless, round-to-oval, craterform ulcer usually on exposed skin area (Fig. 41.42)

LR: a scar with peripheral activity; papules, vesicles, plaques, nodules, in or around previous leishmaniasis healed lesion

Fig. 41.43 Disseminated cutaneous leishmaniasis: multiple pleomorphic lesions, papules, nodules, and ulcers (Photograph courtesy of Dr. Ana Lucia França da Costa, Faculdade de Medicina da Universidade Federal do Piauí, Brazil)

Fig. 41.44 Mucocutaneous leishmaniasis: extensive infiltrated crusted facial plaque, and involvement of nasal mucosa (Photograph courtesy of Dr. Ana Lucia França da Costa, Faculdade de Medicina da Universidade Federal do Piauí, Brazil)

Fig. 41.45 Mucocutaneous leishmaniasis: destructive lesions of mucosal tissues in the upper respiratory tract (Photograph courtesy of Dr. Ana Lucia França da Costa, Faculdade de Medicina da Universidade Federal do Piauí, Brazil)

cutaneous forms can occur in coinfected patients [6, 319]. TL has also been reported to occur during immunologic recovery after ART initiation, as part of the IRIS. Most of these cases occurred 4 months following ART introduction, and the mean baseline (pre-ART) CD4 count was <100 cells/mm^3. VL and PKDL were the most commonly reported clinical manifestations, followed by TL and uveitis [16].

Complementary Examinations

Diagnosis of leishmaniasis is based on criteria that consider epidemiologic data, clinical features, and laboratory test results [32, 319]. In endemic areas the typical presentations of leishmaniasis may be suitable to suggest the diagnosis; nevertheless, it is accurate to have the parasitologic and/or immunologic diagnosis confirmed [319]. Table 41.14 lists the diagnostic tools for TL.

Parasitologic Diagnosis

Definitive diagnosis requires demonstration of the parasite by histology, culture, or molecular analysis of tissue samples, which can be obtained by scraping, fine-needle puncture, or biopsy. The edge of a cutaneous lesion is the most appropriate site for skin biopsy [99]. The so-called touch preparation cytology method (imprint; "touch prep") is useful for obtaining rapid interpretations [319]. To perform Giemsa-stained "touch prep" smears, gently grasp the original biopsy sample with forceps and blot the cut surface onto a paper towel or gauze to remove excess blood; gently press the blotted surface onto a clean glass slide using rolling or circular motions while avoiding compressing tissue; air dry the slides, fix in methyl alcohol, and stain with Giemsa [329]. Direct microscopic examination, in vitro culture, and immunohistochemistry are parasitologic diagnostic methods with variable sensitivity that depends on geographic region, *Leishmania* species, and the clinical form of leishmaniasis [100, 115, 319]. In the TL/immunosuppression-associated and in diffuse leishmaniasis the lesions usually present with a high parasite density, whereas

Table 41.14 Diagnostic tests for leishmaniases

Diagnostic tool	Characteristics	Cutaneous leishmaniasis	Mucocutaneous leishmaniasis
Parasitologic diagnosis[a]			
Direct microscopic examination[b]	Detects *Leishmania* parasites in tissues	High specificity	High specificity
	Does not allow species identification	Variable sensitivity[e]	Low sensitivity
		LR and chronic lesions: scarce parasites on samples	Mucosal lesions: scarce parasites due to strong local immune reaction
Immunohistochemistry	Detects *Leishmania* antigens in tissues	CL/HIV: usually numerous parasites on samples	
	Does not allow species identification		
In vitro culture	Allows species identification		
	Reference laboratory required		
	Time consuming		
Molecular diagnosis with PCR-based methods	Detects *Leishmania* DNA	Highly sensitive and specific	
	Allows species identification	Protocols not standardized	
	Reference laboratory required		
Immunologic diagnosis[c]			
Leishmanin intradermal skin test[d] (Montenegro test)	Evaluates anti-*Leishmania* delayed-type hypersensitivity	Variable specificity[f]	
		High sensitivity	
		Positivity increases clinical suspicion	
		Usually positive in DL, LCL and ML	
		Usually negative in DCL, PKDL, and immunosuppressed CL/HIV	
Serologic tests	Anti-*Leishmania* antibody assays (ELISA; IFAT, IIFA)	Variable specificity[f]	Low sensitivity
		Low sensitivity	Positivity increases clinical suspicion
		TL: limited use	
		TL-HIV: usually negative in immunosuppressed	Useful to monitor relapses

Goto and Lindoso [100], Handler et al. [115], WHO [319]

CL/HIV cutaneous leishmaniasis/HIV coinfection, *DCL* diffuse cutaneous leishmaniasis, *DL* disseminated leishmaniasis (cutaneous), *ELISA* enzyme-linked immunosorbent assay, *IIFA* indirect immunofluorescence assay, *LCL* localized cutaneous leishmaniasis, *LR* leishmaniasis recidiva cutis, *ML* mucosal leishmaniasis, *PCR* polymerase chain reaction, *PKDL* post-kala-azar dermal leishmaniasis

[a]Reference standard for tegumentary leishmaniasis diagnosis

[b]Giemsa staining can be useful to highlight parasites

[c]Do not distinguish between past and present infections

[d]Positive test (≥5 mm diameter) is indicative of cell-mediated immunity; positive results usually appear within 3 months of infection

[e]Sensitivity depends on geographic location, species, and stage of the lesion; multiple parasitologic diagnostic tests recommended for each patient

[f]Possible cross-reactions with *Trypanosomiasis*, deep mycoses, and mycobacteria infections

chronic lesions such as ML and DL have scarce parasites on samples, and repeat biopsies may be necessary [100]. In vitro culture is the best way to isolate parasites; nevertheless, it may be challenging to perform, because *Leishmania* organisms are fastidious [115]. Molecular approaches using PCR-based methods allow the detection of *Leishmania* DNA as well as the identification of *Leishmania* species. PCR methods can detect *Leishmania* DNA in different biological materials, even with a low parasite load; they are highly sensitive and specific, and provide fast results [99]. PCR is the most sensitive approach to confirm mucosal leishmaniasis [319].

Immunologic Diagnosis

Immunologic tests are used as indirect parameters for the diagnosis, and comprise the leishmanin skin test (Montenegro skin test) and serologic assays. Immunologic tests cannot reliably differentiate between past and present infections. They also show variable specificity, because of possible cross-reactivity between *Leishmania* and other infectious agents, such as *Trypanosoma*, mycobacteria, and some fungi [99, 319]. The leishmanin skin test detects anti-*Leishmania* delayed-type hypersensitivity. It consists of an intradermal injection of killed promastigotes; the response is measured after 48 or 72 h and ≥5 mm induration is considered positive [99]. It is more appropriately used in epidemiologic studies but is of little value in the diagnosis of cutaneous leishmaniasis as an isolated tool. It is usually positive in DL, LCL, and ML, whereas it is negative in DCL, PKDL, and immunosuppressed *Leishmania*/HIV-coinfected patients [100]. The more commonly used serologic assays to detect anti-*Leishmania* antibody are the indirect immunofluorescence assay (IIFA) and ELISA. The sensitivity of serologic tests is variable in *Leishmania*/HIV-coinfected patients depending on the antigen preparation used and the host immune status. Some patients might have *Leishmania*-specific committed memory cells preserved, even in the face of HIV immunosuppression, rendering serologic tests of higher sensitivity [100]. The presence of other OI may complicate the clinical diagnosis in HIV/*Leishmania*-coinfected patients. In endemic areas, patients with unusual presentations of TL should be tested for HIV infection [319].

Therapeutic Approach

Prevention of exposure to leishmanial infection relies on reservoir host control in areas with zoonotic transmission and vector control activities, such as indoor residual spraying and/or use of insecticide-treated bed nets. Personal protective measures include minimizing nocturnal outdoor activities, wearing protective clothing, and applying insect repellent to exposed skin (Panel OI HIV NIH Leishmaniasis 2016).

Few systematic data are available on the efficacy of pharmacologic treatments for tegumentary forms of *Leishmania*/HIV coinfection (Panel OI HIV NIH Leishmaniasis 2016). In the general population the treatment may be either local or systemic, whereas in HIV-infected patients only systemic treatment is recommended [100]. The treatment decision is based firstly on the risk–benefit ratio of the intervention for each patient. Amphotericin B is the first-choice agent for VL and TL; both amphotericin B deoxycholate and lipid formulations can be used for the treatment of TL ([32]; Panel OI HIV NIH Leishmaniasis 2016 [319]). Availability, cost, and side effects should be taken into account when choosing between the two agents. Available guidelines recommend different amphotericin B regimens, as shown in Table 41.15 ([32]; Panel OI HIV NIH Leishmaniasis 2016 [319]). The alternative therapeutic agents include pentamidine isethionate and two pentavalent antimonials: meglumine antimoniate (MG) and sodium stibogluconate (SSG). According to WHO recommendations, amphotericin B should be considered as first choice whereas pentavalent antimonials should be reserved only for areas with no significant *Leishmania*-drug resistance and when amphotericin B lipid formulations are unavailable or unaffordable [319]. Both pentavalent antimonials are chemically similar, and their toxicity and efficacy are related to their pentavalent antimony (Sb^{5+}) content: MG solution contains 8.1% Sb^{5+} (81 mg Sb^{5+}/mL), whereas SSG solution contains 10% Sb^{5+} (100 mg Sb^{5+}/mL) (see Table 41.15) [319]. The treatment efficacy varies according to the geographic region, species of *Leishmania*, and clinical presentation (Goto and Lindoso 2010). Because of drug toxicities the pretreatment assessment of cardiac, hepatic, pancreatic, and renal functions is highly recommended [32].

Clinical parameters are used to assess the response to treatment. If clinical cure is not achieved, it is considered as relapse and new treatment should be provided with the same or an alternative regimen [100]. Long-term follow-up is recommended for *Leishmania*/HIV-coinfection, especially in patients whose CD4 count is <200 cells/mm³ (Panel OI HIV NIH

Table 41.15 Treatment for *Leishmania*-HIV coinfection (tegumentary forms)

Drug	Dose/regimen	Full course of treatment	Contraindications and pregnancy risk	Adverse effects
First choice				
Amphotericin B deoxycholate	Brazil: 1 mg/kg, IV, daily	Total cumulative dose at least 1.5 g	Hypersensitivity to amphotericin	Renal toxicity (lower for liposomal formulation); hypokalemia; hypomagnesaemia; acute infusion reactions (e.g., fever, chills, hypotension)
	CDC and WHO: N/A	Duration of therapy may be variable, depending on patient tolerance	Use with caution in decreased renal and cardiovascular function	
		Daily maximum dose 50 mg	Pregnancy risk category B	
Liposomal amphotericin B[a]	Brazil: 1–4 mg/kg/, IV, daily	LCL and DCL: 1–1.5 g total dose		
		ML: 2.5–3 g total dose		
	CDC: 2–4 mg/kg IV	Daily for 10 days or interrupted schedule up to 20–60 mg/kg (total dose)		
	WHO: 3–5 mg/kg IV	Daily or intermittently[d] for 10 doses, up to 40 mg/kg (total dose)		
Alternatives				
Pentavalent antimonials[b]	Brazil (MG): 15 mg Sb^{5+}/kg, IV[c] or IM, daily	CL: 20 days	Cardiac conduction disorder	Anorexia; arthralgia; cardiac toxicity; hepatic toxicity; myalgia; leukopenia; pancreatitis; skin rash
	CDC (SSG): 20 mg Sb^{5+}/kg, IV[c] or IM, daily	ML: 30 days	Renal and hepatic failure	
	WHO (SSG): 20 mg Sb^{5+}/kg, IV or IM[c], daily	28 days	Safety in pregnancy not established	
		10–20 days[e]		
Pentamidine isethionate	Brazil: 4 mg/kg/day, IM or IV, every other day	3– 10 doses for TL[f]	Diabetes mellitus; cardiovascular disease; renal failure; Pregnancy risk category C	Hypoglycemia; hypotension; increased liver enzyme; increased serum creatinine; injection site reaction; leukopenia; renal failure
	CDC: N/A	10 doses for ML caused by *L(V) braziliensis*		
	WHO: 3–4 mg/kg on alternate days	–		
		3 to 4 doses		

Brazilian Health Ministry [32], Goto and Lindoso [100], Panel (2016), WHO [319]

CL cutaneous leishmaniasis, *IM* intramuscular, *IV* intravenous, *MG* meglumine antimoniate, *ML* mucosal leishmaniasis, *N/A* not available, *Sb^{5+}* pentavalent antimony, *SSG* sodium stibogluconate

[a]First-choice therapy according USA guidelines; off-label drug in Brazil

[b]Doses are expressed as mg of pentavalent antimony (Sb^{5+}) content; MG has 81 mg Sb5$^+$/mL; SSG has 100 mg Sb^{5+}/mL

[c]Preferred IV route, especially in thrombocytopenic and undernourished patients

[d]Days 1–5, 10, 17, 24, 31, and 38

[e]There is no evidence for the optimal duration

[f]Three doses for *Leishmania* (*V*) guyanensis; ten doses for *L(V)* braziliensis and *L(L)* amazonensis

Leishmaniasis 2016). Although no published data on efficacy are available, maintenance therapy may be indicated for immunocompromised patients with cutaneous leishmaniasis who have multiple relapses after adequate treatment (Panel OI HIV NIH Leishmaniasis 2016).

The impact of ART on tegumentary forms of *Leishmania*/HIV coinfection has not been studied (Alvar et al. 2008). There are no clinical trials demonstrating superiority of any antiretroviral regimens that allow a specific ART recommendation for patients with *Leishmania*/HIV coinfection [32].

Noninfectious Skin Disorders

Xerosis

Xerosis means skin dryness. It is a frequently found dermatologic disorder in approximately 30% of HIV-infected patients, being also a common cause of pruritus [27, 287, 296, 331]. The pathogenesis of HIV-associated xerosis is unknown, and the following factors may be involved: nutritional status; microcirculation, and changes in both skin sweat and sebaceous glands [42]. Rowe et al. reported decreased cutaneous innervation, peptides, and substance P in the skin of HIV patients with xerosis [267]. Xerosis is clinically characterized by diffuse cutaneous dryness with scales, mainly on the extremities. Xerosis is usually more intense in severely immunosuppressed patients, and patients with atopic status and impaired cutaneous barrier. The most severe cases may evolve into eczema craquelé (Fig. 41.46), whereby fissures and cutaneous barrier breakage occurs and favors secondary infection [72]. There are some studies correlating xerosis to low CD4 count, possibly considered a marker of HIV progression [42]. As part of the management it is important to examine the patient's nutritional condition and CD4 count, besides starting ART. Treatment of xerosis includes mild soaps and topical emollients, especially those with urea and lactic acid.

Fig. 41.46 Eczema craquelé: dry scaling and fissures as a result of severe xerosis

Seborrheic Dermatitis

General Epidemiology

Seborrheic dermatitis (SD) is a recurrent chronic inflammatory dermatosis and one of the most common cutaneous manifestations in HIV-infected patients; it may be noticed in up to 40% of seropositive and in up to 80% of AIDS patients, compared with 3% in the general population [91, 181, 191, 225, 263]. SD occurs in any stage of HIV disease, can be the early presentation of HIV infection, worsens as CD4 count decreases, and may also be a cutaneous marker for HIV infection and disease progression, especially when there is an atypical presentation [167, 222].

Etiopathogenesis

Although the exact cause of SD is not completely clear, sebum production, *Malassezia* metabolism, and individual susceptibility play significant roles in triggering inflammatory and hyperproliferative epidermal responses [276]. *Malassezia* is a normal component of the cutaneous flora, although in SD individuals the yeast possibly causes an unspecified immunologic reaction which triggers an inflammatory cascade, resulting in epithelial changes [92, 276]. The severity of SD in HIV patients besides the lesions worsening in parallel with HIV disease progression may also suggest that SD is associated with host immunologic dysfunction facing HIV infection (Chatzikokkinou et al. 2008; [224]).

Clinical Presentation

SD is characterized by erythematous patches and greasy white-yellowish scaling associated with pruritus of variable intensity. It has a predilection for scalp, eyebrows, forehead, paranasal folds (Fig. 41.47), and retroauricular, presternal, interscapular, and pubic areas. The intertriginous folds may also be involved, especially in obese patients. On the scalp the lesions may vary from a slight scaling to adhering crusted patches, possibly resulting in transient alopecia [51, 270]. Eventually there may be an overlapping of SD and psoriasis clinical aspects [72].

Fig. 41.47 Seborrheic dermatitis: erythema and greasy scales on the face, especially in the nasolabial folds and forehead

On the pigmented skin SD may display hypopigmented annular patches, the so-called petaloid SD, whereby the erythema is less visible and hyperpigmentation is a common finding after resolution of the lesions (Motswaledi et al. 2014). HIV-associated SD may be similar to SD in immunocompetent patients, but is usually more severe or atypical (Chatzikokkinou et al. 2008). In a study by Morar et al., SD caused 12.5% of the erythrodermas in HIV-infected patients [195]. The occurrence of atypical and refractory SD may warn of a possible underlying HIV infection and should prompt HIV testing (Motswaledi et al. 2014).

Complementary Examinations

The diagnosis is usually based on the clinical appearance and topography of the erythematous scaling lesions. A biopsy for histologic study is a resourceful tool on encountering atypical forms of SD.

Therapeutic Approach

SD management aims at reducing the pruritus and the visible signs of disease. Shampoos, topical antifungals, calcineurin inhibitors, and corticosteroids are part of the treatment (Table 41.16). Since SD is a chronic condition, ongoing maintenance therapy is often needed. HIV-associated SD may show itself more extensive resistance to the traditional treat-

Table 41.16 Treatment for seborrheic dermatitis in adults

Scalp seborrheic dermatitis		Facial and body seborrheic dermatitis
Medication	Frequency of use	Frequency of use
Shampoos		
Coal tar shampoo	Twice per week	–
Selenium sulfide shampoo	Twice per week	–
Zinc pyrithione shampoo	Twice per week	–
Topical antifungals		
Ciclopirox 1%	Daily initially, then twice per week	Twice daily for 4 weeks
Ketoconazole 2%	Daily initially, then twice per week	Twice daily for 4 weeks
Topical calcineurin inhibitors	–	
Pimecrolimus 1% cream	–	Twice daily
Tacrolimus 0.1% ointment	–	Twice daily
Topical corticosteroids		
Betamethasone valerate 0.1%	Once daily (lotion)	Once daily (cream)
Fluocinolone 0.01%	Once daily (lotion)	Once daily (cream)
Hydrocortisone 1%		Once daily (cream)
Clobetasol 0.05% shampoo, plus Ketoconazole 2% shampoo	Alternating medications, each twice weekly	

Ang-Tiu et al. [10], Clark [52], Dawson (2007), Dlova and Mosam [72], Firooz et al. [84], Katsambas et al. [135], Moraes et al. [195], Motswaledi et al. (2014), Papp et al. [230], Sampaio et al. [271], WHO [323]

ment, also with more frequent relapses. Symptomatic patients who do not ameliorate under standard treatment should be referred to a dermatologist. For mild scalp SD, the use of shampoos with selenium sulfide, zinc pyrithione, or coal tar may control the symptoms. In case of well-adhered scales emollients can be applied (e.g., mineral oil or petrolatum) at nighttime and removed on the following day [51]. Shampoos must be retained on the scalp for a minimum of 5 min to assure the appropriate scalp exposure to the active ingredient [51]. For long-term control, antifungal shampoos with 2% ketoconazole or 1% ciclopirox can be used on a daily basis, or at least twice or three times a week until remission. The weekly maintenance of these shampoos can prevent recurrences. Depending on the intensity of the scalp inflammation topical corticosteroids may be necessary, although long-term use must be avoided because of adverse effects. For facial and body SD, therapeutic tools include topical antifungals, corticosteroids, and calcineurin inhibitors (pimecrolimus, tacrolimus). Owing to their efficacy, limited adverse effects, and reasonable cost, topical antifungals are the preferred agents for initial SD treatment of the face and body, as well as maintenance therapy [51]. Low- or mid-potency topical corticosteroids alleviate symptoms of the extremely inflammatory SD, showing an efficacy comparable with that of antifungal agents [84, 134]. Because of their safety profile, corticosteroids are regarded as a second-line choice for SD, and their long-term use is contraindicated on account of the risk of cutaneous atrophy and telangiectasias [51]. Topical calcineurin inhibitors have shown similar efficacy to antifungals and topical corticosteroids, but with a lower risk for adverse effects [10, 229]. Facial SD in HIV-infected patients has been successfully managed with topical pimecrolimus regardless of patients' immunologic status, with no changes in CD4, CD8, or viral load counts throughout treatment [194]. Patients undergoing ART may show decreased SD severity and frequency, although there have been reports of aggravation during IRIS [288, 321].

Psoriasis

General Epidemiology

Psoriasis is a chronic papular scaling dermatosis affecting 2–3% of the world's population, and in HIV-patients its prevalence is similar or a little higher [168]. It may be associated with systemic manifestations, corresponding to an autoimmune disorder resulting from keratinocyte proliferation, T-cell mediation, possible genetic susceptibility, and environmental factors [196, 311]. Psoriasis may appear in all phases of HIV infection, although it usually worsens and may become treatment-resistant in the advanced phase. There is a correlation between low CD4 count and psoriasis severity [168]. Moreover, many of these patients are affected with significant psoriatic arthritis [189].

Etiopathogenesis

The pathogenesis of HIV-associated psoriasis seems to be paradoxical, since psoriasis is a T-helper 1 (Th1)-mediated disorder, and there is Th2 immunologic predominance in the HIV-associated advanced disease. Also intriguing is the fact that psoriasis, which is mediated by T-cell activation, becomes more severe with HIV progression, when CD4 count is low [196]. It has been hypothesized that the immunologic deregulation resulting from HIV infection may trigger or exacerbate an existing psoriasis in genetically predisposed individuals [83]. The causal scenario for such a paradox is possibly related to many factors: genetic susceptibility; autoimmunity; destruction of regulatory T CD4 cells by HIV; quantitative increase of memory T CD8 cells and interferon-γ production, especially at the late stage of HIV disease; action of HIV proteins and other pathogens, as the superantigens; and also a direct epidermal proliferative effect of HIV [196, 233].

Clinical Presentation

The typical cutaneous pattern of psoriasis is characterized by circumscribed, erythematous, dry, and scaling plaques of different sizes [311]. Scales are typically silvery and peeling in layers, and when removed tiny bleeding points can be seen (the so-called Auspitz sign). Symmetric lesions are most localized on limbs, abdomen, trunk, scalp, and nails. The lesions may show different patterns: guttata (small drops), follicular, annular, discoid (solid patches) (Fig. 41.48), rupioid (very thick crusts) (Fig. 41.49), and inverse (psoriasis in the flexural areas), among others. The inverse-pattern psoriasis displays erythema and maceration, instead of the typical dry scaling, on the moist flexural areas (Fig. 41.50) and genitals (Fig. 41.51) [196]. Nails are usually affected by distal onycholysis (Fig. 41.51), pitting, oil

Fig. 41.48 Discoid psoriasis: symmetric erythematous scaling patches and plaques

Fig. 41.49 Rupioid psoriasis: large and very thick crusts on limbs

Fig. 41.50 Inverse psoriasis: perianal erythema and maceration

Fig. 41.51 Psoriasis: erythematous annular lesions on the genital area resembling tinea; and onycholysis (Photograph courtesy of Dr. Andre Avelino Costa Beber, Hospital Universitário de Santa Maria, Brazil)

spots, or subungual debris, and hyperkeratosis mimicking onychomycosis. Psoriasis in palms and soles may present as well-circumscribed heavy hyperkeratosis and fissures (Fig. 41.52). Up to 40% of patients with psoriasis may have evidence of arthritis, which presents a variety of different patterns: monoarthritis; oligoarthritis; involvement of the distal interphalangeal joints; and a rheumatoid arthritis-like picture with multiple joints involved or axial disease producing symptoms similar to ankylosing spondylitis [58].

In HIV-associated psoriasis, several morphologic types may coexist in the same patient [217] (Box 41.10). The clinical phenotypes of HIV psoriasis show variable prevalence. In a series in the United States the most common form was patchy psoriasis, whereas in South Africa the erythrodermic variant was prevalent, probably associated with advanced HIV stages [196, 217]. Erythrodermic psoriasis is a severe form that can have a sudden appearance or follow a chronic course (Fig. 41.53). Patients with erythrodermic psoriasis can develop generalized skin failure associated with mortality [196].

Reactive arthritis (Reiter's syndrome) is a seronegative spondyloarthropathy characterized by arthritis, urethritis, and conjunctivitis. Its prevalence is high in HIV patients [196]. Both psoriasis and reactive arthritis can be triggered by infections and might be part of a disease continuum [74]. The most frequently seen presentation is seronegative peripheral arthritis [2]. The classic cutaneous presentation seen in more than half of patients includes palmoplantar psoriasis-like plaques (keratoderma blenorrhagicum) (Fig. 41.54) and circinate balanitis [196]. Studies evaluating HIV-associated reactive arthritis have found human leukocyte antigen (HLA)-B27 in 80–90% of Caucasians while studies of Africans have found nearly all to be HLA-B27 negative [78].

Complementary Examinations

Usually the diagnosis is based on the clinical appearance and topography of the psoriatic scal-

Fig. 41.52 Psoriasis in soles: well-circumscribed heavy hyperkeratosis and fissures (Photograph courtesy of Dr. Andre Avelino Costa Beber, Hospital Universitário de Santa Maria, Brazil)

Fig. 41.53 Erythrodermic psoriasis

ing lesions. A biopsy for histologic study is a resourceful tool in face of atypical or erythrodermic psoriasis.

Therapeutic Approach

Given the fact that psoriasis has no cure, the aim of treatment is the provision of a reasonable

Box 41.10 Clinical Characteristics of HIV-Associated Psoriasis

- Sudden onset
- Palmoplantar keratoderma
- Involvement of skin folds
- Pustular forms
- Severe nail dystrophy
- High frequency of arthritis

Table 41.17 Treatment for HIV-associated psoriasis according severity

	First choice	Second choice
Mild to moderate psoriasis	Topical therapy: calcipotriol, corticosteroids, tazarotene, combined calcipotriol + betamethasone dipropionate	–
Moderate to severe psoriasis	UV-therapy (UVB, PUVA) Antiretrovirals	Oral retinoids
Severe refractory psoriasis	Cyclosporine, methotrexate, TNF-α inhibitors, hydroxyurea	

Menon et al. [189]
PUVA psoralen plus ultraviolet A, *TNF* tumor necrosis factor, *UV* ultraviolet

improvement of the lesions. There are no randomized placebo-controlled trials evaluating the safety and efficacy of treatments for HIV-associated psoriasis. The general principles of management of psoriasis and treating HIV apply [196]. Evidence based therapeutic recommendations for psoriasis management in HIV patients were developed by the Medical Board of the National Psoriasis Foundation, and are summarized in Table 41.17 [189]; Table 41.18 lists pharmacologic options and regimens. The published systematic reviews for topical treatments for psoriasis are not specifically targeted to HIV-infected patients, but could be used for them. For chronic plaque psoriasis, corticosteroids perform at least as well as vitamin D analogs (calcitriol,

calcipotriene/calcipotriol), and are associated with a lower incidence of local adverse events. Although topical vitamin D analogs are effective as monotherapy for some patients, a systematic review found that combination therapy with a topical corticosteroid is more effective than either treatment alone [180]. For refractory HIV-associated psoriasis treatment is challenging, and should be tailored to patients based on disease severity and immunologic status. Close monitoring for potential adverse events of systemic therapy is paramount [189]. HIV patients who are adherent to medication regimens and frequent monitoring, and have failed other treatment modalities, could be considered for treatment with tumor necrosis factor α (TNF-α) inhibitors. However, given the limited evidence and the substantial risks associated with their use, TNF-α inhibitors should be reserved for patients with very refractory psoriasis or with debilitating psoriatic arthritis. In addition, these patients should receive optimal ART and close monitoring [94]. Patients with unknown HIV status and with psoriasis unresponsive to therapy should prompt HIV testing.

Fig. 41.54 Reactive arthritis with psoriasis-like lesions, severe onychodystrophy; and involvement of the distal interphalangeal joints in in an HIV patient as part of the immune reconstitution inflammatory syndrome (IRIS)

Papular Pruritic Dermatoses

Among the papular pruritic dermatoses related to HIV infection, two entities are as yet not well differentiated: papular pruritic eruption

Table 41.18 Pharmacologic treatments for psoriasis and psoriatic arthritis

Drug	Dosage	Monitoring	FDA pregnancy category
Topical therapies	*In affected areas*		
Corticosteroids	Once or twice daily	–	
Tacrolimus; pimecrolimus	Twice daily	–	C
Tazarotene	Once daily	–	X
Vitamin D analogs: calcitriol; calcipotriene (calcipotriol)	Twice daily	–	C
Systemic therapies			
Acitretin	10–50 mg orally per day	Renal function tests, LFTs, lipid panel, and CBC every 1–2 weeks until levels stabilize (typically 4–8 weeks)	X
Cyclosporine[a]	2.5–5.0 mg/kg/day, orally in two divided oral doses	Blood pressure; CBC; LFTs; lipid panel; and magnesium, uric acid, blood urea nitrogen, creatinine, potassium levels every 2 weeks for the first 3 months of therapy, then monthly if stable	C
Methotrexate[a]	7.5–25 mg orally per week	LFTs, renal function tests, CBC, and platelet count every 1–2 months	X

Patel and Weinberg [234], Weigle and McBane [311]
CBC complete blood count, *FDA* US Food and Drug Administration, *LFTs* liver function tests
[a]Useful in patients with psoriatic arthritis

(PPE) and eosinophilic folliculitis (EF). Both are chronic pruritic inflammatory dermatoses usually seen in the advanced phase of HIV infection, although they may also occur as part of IRIS [28, 76, 111, 246, 278, 289]. According to the WHO criteria, the presence of associated PPE defines HIV disease as clinical stage 2, also being a parameter for ART initiation [318]. There are major gaps in the understanding of EF and PPE regarding etiology, natural history, and their role as potential prognostic markers of HIV. PPE mainly affects HIV-infected people living in tropical regions, whereas EF has been described in patients living in developed countries [76, 265]. EF is prevalent in body areas of major concentration of sebaceous glands where the *D. folliculorum* mite is common (Fig. 41.55); PPE, on the other hand, affects mainly the limbs (Fig. 41.56) where insect bites are frequent [278]. The etiopathogenesis hypotheses consider that both diseases may involve deregulated immunologic reactions: in EF a reaction against an unknown antigen, and in PPE a reaction against insect bites, although no specific organism has been identified to date ([80, 253]; Rosatelli et al. 2001; [265]). In a recent study by Chua et al., the presence of PPE in HIV-infected persons undergoing ART was associated with high HIV viral loads at baseline (pre-ART). It has been suggested that the pretreatment of high HIV viremia may have persistent effects even after starting ART and after achieving virologic suppression. The mechanism of this effect on PPE is still unknown. In the same study, PPE in ART-treated HIV-infected persons was not associated with the immune activation markers measured, including CD4 T-cell gains and CD8 T-cell activation [50]. Afonso et al. have suggested that these two entities could possibly be distinguished by histopathologic and immunohistochemical features in addition to clinical characteristics, and that they could both be within the spectrum of the same disease [3]. Since the sole clinical diagnosis is not ideal, a lesion biopsy is important for diagnostic

Fig. 41.55 Eosinophilic folliculitis: pruritic follicular edematous papulovesicles with on face and trunk (central body distribution)

Fig. 41.56 Papular pruritic eruption: skin-colored prurigo-like papules, excoriations, and postinflammatory hyperpigmentation (peripheral location)

confirmation [50]. To date, there have been no randomized clinical trials aimed at therapeutic interventions for EF or PPE. Table 41.19 lists the main characteristics and proposed treatments for EF and PPE.

Antiretroviral Therapy-Associated Manifestations

Cutaneous Toxicities of Antiretroviral Therapy for HIV

The expanded access to ART over the past three decades has led to substantial declines in HIV-related morbidity and mortality. However, multidrug therapy for HIV infected patients is complicated by numerous adverse effects including drug-related toxicities, drug interactions, and IRIS. HIV-infected patients are at higher risk for developing drug-related toxicities than HIV-negative counterparts [121]; and up to 80% of them may experience adverse drug reactions at some point during their therapy, presumably as a result of immune dysregulation, altered drug metabolism, and/or polypharmacy [29, 279]. In addition to the inherent risk

Table 41.19 Summary of characteristics of HIV-associated eosinophilic folliculitis and pruritic papular eruption

	Eosinophilic folliculitis	Pruritic papular eruption
Demographics	Patients most living in developed countries	Populations living in the tropics
Clinical picture	Pruritic follicular edematous papulovesicles, pustules (not predominant)	Pruritic skin-colored papules, pustules rare, prurigo-like nodules, excoriations, postinflammatory hyperpigmentation, scarring
Anatomic pattern	Central distribution: face, neck, postauricular, upper arms, trunk	Peripheral location, or generalized: symmetric, distal extremities, face, trunk, rare on palms and soles
Histologic picture	Folliculocentric lymphocytic and eosinophilic infiltrate; absence of microorganisms, number of mast cells higher than in PPE	Similar to hypersensitivity reaction to insect bites: nonfolliculocentric wedge-shaped dense perivascular and interstitial lymphocytic infiltrates with many eosinophils
Laboratory data	↑ IgE, eosinophilia	↑ IgE, eosinophilia
	CD4 <250/mm^3	CD4 <100/mm^3
	↑ serum levels of CCL17, CCL26, CCL27	↑ CD8 T cells
		↑ HIV viremia at ART initiation, independent of CD4 count
Improvement under ART	Yes	Yes
Marker for immunosuppression	Yes	Yes; highly predictive of HIV infection in the tropics
Occurrence as part of IRIS	Yes	Yes
Treatment	ART is the primary treatment	ART is the primary treatment
	Potent topical steroids, for the duration of persistent symptoms	Potent topical steroids, for the duration of persistent symptoms
	Topical 1% tacrolimus ointment	Promethazine 25 mg bid
	Topical permethrin 5%	Thalidomide 100 mg daily
	Oral antihistamines	Dapsone 100 mg daily
	Oral metronidazole 250–500 mg bid	Pentoxiphylline 400 mg bid
	Itraconazole 200–400 mg daily	Narrowband ultraviolet B phototherapy
	Oral isotretinoin 20–80 mg/day, 6–8 weeks	
	Dapsone 100 mg daily	
	Ultraviolet B phototherapy	

Afonso et al. [3], Bellavista et al. [22], Chua et al. [50], Eisman [76], Farsani et al. [80], Lakshmi et al. [150], McCalmont et al. [185], Navarini et al. [208], Rajendran et al. [246], Resneck et al. [253], Rosatelli and Roselino [264], Rosenthal et al. [265], Serling et al. [278], Wernham et al. [315], WHO [321], Yokobayashi et al. [328]

ART antiretroviral therapy, *bid*, twice daily, *CCL17* chemokine ligand 17 (thymus and activation regulated chemokine), *CCL26* chemokine ligand (chemotactic for eosinophils and basophils), *CCL27* chemokine ligand 27 (cutaneous T cell-attracting chemokine), *CD4* CD4+ T cell, *CD8* CD8+ T cell, *IgE* immunoglobulin E, *IRIS* immune reconstitution inflammatory syndrome

of cutaneous side effects from the medications themselves, HIV patients are at increased risk for immune-mediated cutaneous reactions to medications of any type, likely because of immune dysregulation [128]. Yang et al. have proposed that HIV infection could represent a predisposition for severe drug reaction by depletion of CD4 T cells and loss of regulatory T cells in the skin, which subsequently leads to an upregulation of cytotoxic CD8 T cells [327]. The adverse reactions may range from life-threatening disorders to cosmetic concerns contributing to increased morbidity and often also leading to discontinuation of ART. Some of these toxicities are family- or even drug-specific (Table 41.20).

ART-associated lipodystrophy syndrome consists of changes in body fat composition usually in association with metabolic abnormalities. These disorders are a side effect of the nucleoside reverse transcriptase inhibitors (NRTI), particularly stavudine and the combination of stavudine and didanosine with or without protease inhibitor (PI) therapy, and the non-nucleoside reverse tran-scriptase inhibitor (NNRTI) efavirenz [128]. The anatomic characteristics include fat loss in the face (Fig. 41.57), limbs, and buttocks, and the accumulation of dorsocervical ("buffalo hump") and abdominal visceral fat and gynecomastia [104, 310]. The metabolic abnormalities (insulin resistance, hyperinsulinemia, hyperglycemia, and dyslipidemia) can put patients at risk for pan-

Table 41.20 Antiretroviral medications and associated cutaneous reactions

Antiretroviral medications	Cutaneous reactions
Nucleoside reverse transcriptase inhibitors	
Abacavir (ABC)	Skin rash (1–10%), AHR (often described as "maculopapular," but descriptions of urticaria, diffuse erythema, erythema multiforme, or targetoid skin lesions have also been included)
Didanosine (ddI)	Lipodystrophy; pruritus (≤7–9%), skin rash (≤7–9%), xerostomia
Emtricitabine (FTC)	Hyperpigmentation (children: 32%; adults: 2–4); skin rash (17–30%; includes hypersensitivity reaction, maculopapular rash, pruritus, pustular rash, vesiculobullous rash)
Lamivudine (3TC)	Skin rash (5–9%)
Stavudine (d4T)	Skin rash (18–30%), lipodystrophy
Zalcitabine (ddC)[a]	Skin rash (dose-related morbilliform exanthemas, 2%), occasional hypersensitivity syndromes
Zidovudine (AZT, ZDV)	Skin rash (children 12%), nail and mucocutaneous hyperpigmentation
Nucleotide reverse transcriptase inhibitor	
Tenofovir (TDF)	Skin rash (includes maculopapular, pustular, vesiculobullous; pruritus; or urticaria: 5–18%), pruritus (16%)
Non-nucleoside reverse transcriptase inhibitors	
Delavirdine (DLV)	Pruritic rash (18–50%), skin rash (16–32%), desquamation, erythema multiforme, fungal dermatitis, SJS
Efavirenz (EFV)	Skin rash (5–26%), pruritus (≤9%), SJS
Etravirine (ETR)	Skin rash (≥grade 2: 10–15%), hyperhidrosis, gynecomastia, lipohypertrophy, DRESS, SJS, TEN
Nevirapine (NVP)	Skin rash (1–7%; grade 1/2: 13%; grade 3/4: 2%), lipodystrophy, angioedema, DIHS, SJS, TEN, acute generalized exanthematous pustulosis, ulcerative stomatitis
Rilpivirine (RPV)	Skin rash (3–6%)
Protease inhibitors	
Amprenavir (APV)[a]	Self-limited maculopapular rash (20% to 28%), SJS (1%)
Atazanavir (ATV)	Skin rash (adults 3–21%; median onset: 7 weeks; children 14%), asymptomatic jaundice and scleral icterus, DIHS, SJS
Darunavir (DRV)	Skin rash (children: 5–19%; adults: 6–7%)
Fosamprenavir (FPV)	Skin rash (16%), SJS
Indinavir (IDV)	Pruritus (4%), skin rash (1%), lipodystrophy, acute porphyria, SJS
Lopinavir (LPV)	Skin rash (≤28%), pruritus (12%), acne vulgaris (4%), diaphoresis (2–3%), SJS, TEN
Lopinavir/ritonavir boosting (LPV/r) = Kaletra®	Skin rash (children 12%; adults ≤5%), skin infection (3%, including cellulitis, folliculitis, furuncle), SJS, TEN
Nelfinavir (NFV)	Skin rash (1–3%)
Ritonavir (RTV)	Skin rash (≤28%), pruritus (12%)

Table 41.20 (continued)

Antiretroviral medications	Cutaneous reactions
Saquinavir (SQV)	Pruritus (3%), rash (3%), dry lips/skin (2%), eczema (2%), verruca
Tipranavir (TPV)	Rash (children 21%; adults 3–10%)
Fusion inhibitors	
Enfuvirtide (T-20)	Injection site reactions[b] (98%), injection site infection (children: 11%, adults: 2%), folliculitis (2%), generalized rash, hypersensitivity reaction
Integrase inhibitors	
Dolutegravir (DTG)	Pruritus (<2%)
Elvitegravir (EVG)	Skin rash (<2%)
Raltegravir (RAL)	Skin rash with eosinophilia and systemic symptoms (DIHS) <2%
CCR5 antagonists	
Maraviroc	Skin rash (11%), folliculitis (4%), pruritus (4%), acne vulgaris (3%), benign skin neoplasm (3%), alopecia (2%), erythema (2%), tinea (4%)

Bartlett [20], Fletcher [85], Introcaso et al. [128, 129], Phillips and Mallal [238]

AHR abacavir hypersensitivity reactions, *DIHS* drug-induced hypersensitivity syndrome, DRESS drug rash with eosinophilia and systemic symptoms, *SJS* Stevens–Johnson syndrome, *TEN* toxic epidermal necrolysis

[a]No longer marketed in most countries

[b]May include at injection site: erythema, induration, ecchymosis, nodule, pruritus, pain

creatitis at any point during therapy and increase their risk of atherosclerotic disease over years of treatment [104, 128]. Morbilliform rashes usually present as a pruritic erythematous maculopapular eruption approximately 2–10 days after starting the medication. NNRTI are the most frequent class of antiretrovirals to cause morbilliform exanthems. Besides the NNRTs, other classes of antiretrovirals and drugs used for treatment of OI can also trigger skin rashes, e.g., sulfonamides, trimethoprim, dapsone, penicillins, cephalosporins, quinolones, ketoconazole, and clindamycin [29, 179]. Most rashes are mild and do not require medication discontinuation, and most resolve quickly during continued administration. However, the implicated drug should be stopped if the rash is associated with fever, blistering, oral mucous membrane involvement, or arthralgias (e.g., suspected hypersensitivity secondary to nevirapine or abacavir). Morbilliform eruptions related to nevirapine may become severe and be associated with systemic hypersensitivity reactions [129]. Abacavir can lead to serious and sometimes fatal hypersensitivity reactions (AHR) with multiple organ involvement. AHR typically presents within the first 6 weeks of treatment (median time of 9 days) with a combination of symptoms, including fever, rash, gastrointestinal disturbances, and

Fig. 41.57 Lipodystrophy: severe fat loss in the face

other constitutional symptoms. [128]. AHR is strongly associated with HLA-B*5701 allele, and genetic screening prior to abacavir exposure has reduced the incidence of hypersensitivity

reactions. This association has been present across racial groups in Asia, Europe, Latin America, and the Unites States; nevertheless, pharmacogenetics of drug reactions are drug and population specific [156]. In a large study performed in Uganda, however, HLA-B*5701 was not significantly associated with clinically diagnosed AHR in African patients [204]. It is mandatory to discontinue abacavir if a hypersensitivity reaction is suspected. Reintroduction of abacavir can result in life-threatening or fatal hypersensitivity reactions, even in patients who have no history of hypersensitivity to abacavir therapy [128]. IRIS occurs during the initiation of ART while is not a cutaneous toxicity relating to a specific antiretroviral medication. Given its frequent skin manifestations, IRIS must be distinguished from drug reactions [129, 282].

Immune Reconstitution Inflammatory Syndrome

The use of ART in HIV-infected patients results in reconstitution of the immunologic system and recovery of immunologic response against opportunistic pathogens. However, some patients undergo a worsening of the clinical condition. The restoration of the immunologic reaction against living or dead opportunistic pathogens and many antigens results in immunopathologic damage to the infected tissues, and systemic inflammatory reactions. The term "immune reconstitution inflammatory syndrome," or IRIS, describes a collection of inflammatory disorders associated with paradoxical worsening of pre-existing infectious and noninfectious disorders following the initiation of ART [89, 309]. The syndrome is usually identified during the early months, although it may occur from weeks to years after the start of ART [170]. IRIS incidence is considerably variable among the studies. In controlled studies the reported incidence is up to 25% of patients undergoing ART and varies according to the duration of ART [170]. Skin diseases are very common in HIV-infected patients, and the skin is the organ where IRIS often manifests itself, accounting for 52–78% of all reported events [126, 223, 251]. A great variety of dermatologic

presentations has been described, both infectious and noninfectious. Most authors consider as IRIS any newly dermatologic event occurring after ART initiation, whereas other authors used the term only to describe paradoxical or atypical events [223].

Etiopathogenesis

The immunopathogenesis of IRIS is not clear and involves a combination of factors. IRIS results from a deregulated immunologic reaction to a variety of antigenic stimuli following the initiation of ART [280]. Common immunopathologic characteristics may direct IRIS, although there are specific ways depending on the affected tissue and the involved antigens. In infections the antigenic stimulus can act by means of intact or dead viable organisms and their trace antigens, whereas in noninfectious causes there is involvement of innate autoimmunity against several antigens [170, 176].

Throughout the ART-induced immunologic recovery, chronic activation is a critical factor in the complex interaction between HIV and the immune system. Many components may have a role in the IRIS-exacerbated immune reaction: cell proliferation induced by lymphopenia; quantitative and functional reconstitution of immune cells; redistribution of lymphocytes; impaired T-cell regulatory function; changes in the Th-cell profile; high antigenic exposure; and host genetic susceptibility, all favoring a systemically activated immunologic environment and higher availability of proinflammatory cytokines and circulating chemokines [176, 280]. Such a proinflammatory milieu can be further overwhelmed by OI which activate the innate immune system, allowing recognition of pathogens through molecular patterns released from host cells following tissue injury and necrotic cell death [176]. Chronic systemic immune activation, particularly in severely immunosuppressed patients with OI, affects the immune environment in which immune recovery will emerge. Ongoing research has shed some light on these diverse reaction patterns, but has also engendered new questions.

Risk Factors: IRIS affects mainly HIV patients who initiate ART with a status of

Table 41.21 Risk factors for IRIS associated to HIV

Host-related	Low CD4 count at initiation of ART
	OI or TB prior to ART initiation
	Genetic predisposition: e.g., HLA-A, -B44, -DR4 (associated with herpes virus IRIS);TNFA-308*1, IL6-174*G (associated with mycobacterial IRIS)
	Paucity of immune response at OI diagnosis (in the case of C-IRIS)
Pathogen-related	High pre-ART HIV viral load
	Degree of dissemination of OI/burden of infection (e.g., TB, KS, cryptococcosis)
Treatment-related	Shorter duration of OI treatment prior to starting ART (paradoxical IRIS)
	Rapid suppression of HIV viral load

Walker et al. [309]

ART antiretroviral therapy, *IL6* interleukin-6, *C-IRIS* cryptococcal-associated IRIS, *IRIS* immune reconstitution inflammatory syndrome, *KS* Kaposi's sarcoma, *OI* opportunistic infection, *TB* tuberculosis

advanced immunosuppression, having low CD4 count and high viral load, as well as nondetected microorganisms and other antigens; and resulting in unexpected clinical manifestations. Table 41.21 lists risk factors for HIV-associated IRIS [309].

Clinical Presentation

IRIS is a heterogeneous condition. Clinical and laboratory studies over the two latest decades have defined three categories [44]:

1. Inflammatory disease or cancer resulting from the recovery of an immune reaction against an opportunistic pathogen that causes localized or systemic impairment and can show itself in two ways:
   (a) An IRIS characterized by an exaggerated inflammation and/or atypical inflammation in patients with an already treated OI (paradoxical IRIS), or a subclinical infection (unmasking IRIS).
   (b) A disease of which the presentation cannot be differentiated from the disease typical events over the first 3 months of ART, such as tuberculosis; herpes zoster, and crises of hepatitis caused by the hepatitis B virus (HBV) and the hepatitis C virus (HCV).

2. Autoimmune diseases associated with the immunologic reconstitution, e.g., Graves' disease.
3. Immune-mediated inflammatory diseases and associated with the immunologic reconstitution, e.g., sarcoidosis.

In the paradoxical forms of IRIS, symptoms and signs associated with a known and eventually treated OI recur or severely worsen despite the previous favorable response to therapy, before ART initiation [309]. The unmasked IRIS concept is less defined than the paradoxical IRIS. In paradoxical IRIS a new OI is present with an intensified inflammatory component after the start of ART [309].

Dermatologic IRIS

Dermatologic IRIS represents around half of the IRIS cases in many series, and has been described in association with a wide range of infectious, inflammatory, tumoral, and autoimmune disorders [89, 126, 152, 155, 170, 223]. Usually the condition is associated with mycobacterial, chronic viral, and invasive fungal infections, but the spectrum of the described infections is still expanding (Table 41.22) [152, 153]. Dermatologic manifestations of IRIS comprise genital herpes, herpes zoster, molluscum contagiosum (Fig. 41.58), warts, cutaneous lesions by cytomegalovirus, Kaposi's sarcoma, and fungal infections such as histoplasmosis. The immunologic reconstitution in HIV patients may also be associated with inflammatory and autoimmune diseases, such as sarcoidosis. However, the immunopathogenesis of these diseases seems to be different from the infectious IRIS [89].

Complementary Examinations

IRIS lacks a precise case definition, unequivocal markers and a definitive diagnostic test. Since there are no well-established criteria for the diagnosis of IRIS, a combination of findings is usually necessary to guide clinical suspicion. The clinical diagnosis of IRIS should be considered when inflammatory signs or symptoms occur between 4 and 8 weeks after initiation of ART, reinstatement of an interrupted regimen, or change to a more effective regimen after

Table 41.22 Pathogens and key clinical features of associated IRIS

Condition	Clinical features of IRIS
Pathogen-associated	
Bacteria	
Mycobacterium tuberculosis	Fever, lymphadenitis, cutaneous tuberculosis
Nontuberculous mycobacteria	Fever, lymphadenitis (painful/suppurative), cutaneous lesions: papules, plaques, nodules, abscess
Mycobacterium avium-intracellulare	
Mycobacterium genavense	
Mycobacterium kansasii	
Mycobacterium scrofulaceum	
Mycobacterium xenopi	
BCG	Vaccine associated; local reaction, lymphadenitis
Mycobacterium leprae	Typically tuberculoid or borderline forms, type 1 reactions, neuritis, lepromatous reaction during leprosy and IRIS has similarities
Other	
Chlamydia trachomatis	Reiter's syndrome
Viral	
Herpes viruses	
CMV	Mucocutaneous ulceration
VZV	Dermatologic reactivation (shingles)
HSV-1, HSV-2	Mucocutaneous ulceration
HHV-8	Kaposi's sarcoma (KS)/IRIS; exacerbations of KS can result in tumor enlargement, new lesions, inflammation, and edema
Polyomaviruses	
Molluscum contagiosum virus	Acute new or recurrent cutaneous papules with florid/extensive distribution
HPV	Warts (acute recurrence/relapse or enlargement)
Fungal	
Cryptococcus neoformans	Cutaneous papules, nodules, soft tissue inflammation
Histoplasma spp	Papular/nodular rash
Candida spp	Typically unmasking; mucocutaneous (oral/oesophageal)
Tinea corporis	Inflammatory cutaneous presentation

Table 41.22 (continued)

Condition	Clinical features of IRIS
Malassezia spp	Immune recovery folliculitis
Sporotrichosis	Cutaneous disseminated sporotrichosis; ulcerated lesions
Parasitic	
Leishmania spp	
Leishmania major	Cutaneous, uveitis
Leishmania infantum	Post-kala-azar dermal leishmaniasis, visceral leishmaniasis
Leishmania braziliensis	Cutaneous, mucosal
Nonpathogen-associated	
Autoimmune	
Polymyositis	May occur as a new presentation, or an exacerbation of existing autoimmune condition
SLE	
Cutaneous chronic lupus	
Relapsing polychondritis	
Dermatologic	
Acne	Inflammatory presentation
Demodex folliculitis	
Eosinophilic folliculitis	
Seborrheic dermatitis	
Pruritic papular eruption	
Psoriasis	
Other	
Sarcoidosis	New or recurrent granulomatous inflammation, typically late (around 12 months post-ART initiation) in patients with CD4 counts <200 cells/mm^3; typically pulmonary presentation, but may be cutaneous (erythema nodosum, papular lesions) and/or intra-abdominal
Tattoo and foreign body reaction	Granulomatous reaction

Huiras et al. [126], Manzardo et al. [170], Sharma and Soneja [280], Walker et al. [309]

ART antiretroviral therapy, *BCG* Bacillus Calmette–Guérin, *CMV* cytomegalovirus, *GUD* genital ulcer disease, *HSV* herpes simplex virus, *HHV-8* human herpes virus 8 (Kaposi's sarcoma virus), *HPV* human papilloma virus, *IRIS* immune reconstitution inflammatory syndrome, *NTM* nontuberculous mycobacteria, *OI* opportunistic infection, *SLE* systemic lupus erythematosus, *VZV* Varicella zoster virus

Fig. 41.58 Molluscum contagiosum: sudden appearance of countless lesions as a result of immunologic recovery after antiretroviral therapy initiation

treatment failure [33]. The only reliable predictors of IRIS risk are a low CD4 count and a pre-existing OI [89, 281]. The International Network for the Study of HIV-associated IRIS (INSHI) published a consensus to define C-IRIS and TB-IRIS cases [112, 186]. The definitions are appropriate for usage in healthcare centers with limited resources, since CD4 cells and HIV viral load counts are not part of the criteria. Currently there are no consensual case definitions for other forms of IRIS [157]. Shelburne and colleagues have proposed clinical criteria for IRIS, which are displayed in Box 41.11 [281]. In places where resources and laboratory support are limited, IRIS will be an exclusion diagnosis after failure of treatment of other conditions [309].

Therapeutic Approach

Appropriate IRIS management requires acknowledgement of the condition and exclusion of differential diagnoses, especially additional resistant infections and OI. Because of the heterogeneity of IRIS in terms of underlying infection, clinical presentation, and severity, the management should be individualized. When IRIS is suspected the diagnosis must be prioritized and the OI treatment optimized. ART should be interrupted only if IRIS is imminently life-threatening [187]. In most cases, IRIS resolution is spontaneous, only requiring symptomatic treatment such as non-steroidal anti-inflammatory drugs. Systemic corticosteroid therapy should be used only in severe cases after a careful risk-benefit consideration. Oral prednisone can be prescribed at a 1–2 mg/kg dose, or equivalent, for 1–2 weeks, with subsequent dose tapering. When considering corticosteroid treatment, clinicians should be aware of the side effects of corticosteroids and only use them when the diagnosis of IRIS is certain. In viral forms of IRIS, corticosteroids are generally avoided [187]. According to small series of case reports, thalidomide, which has been shown to inhibit TNF-α production in vitro, could be beneficial for patients who experience IRIS and do not respond favorably and quickly to corticosteroids. Thalidomide may be indicated at a 100–200 mg/day dose [35, 273]. Since the higher risk of IRIS is associated with low CD4 cell count at the time of ART initiation, IRIS events could be preventable with timely initiation of ART, before patients are at risk of OI and advanced immunodeficiency [203]. It is worth pointing out that IRIS has three rules: (1) anything is possible; (2) nothing is as it was in the pre-ART era; (3) IRIS does not mean that ART has failed. In addition, the patients usually have a good prognosis [122].

Neoplastic Disorders

Kaposi's Sarcoma

Described for the first time in 1872 by Moritz Kaposi, a Hungarian dermatologist, Kaposi's sarcoma (KS) is an angioproliferative tumor caused by the human herpesvirus 8 (HHV-8), also known as Kaposi sarcoma herpesvirus (KSHV). Before the AIDS pandemic, KS was considered a rare disease seen mainly in countries around the Mediterranean Sea (classic KS) and in several African countries (endemic KS). In 1981, a disseminated and fulminant form of KS (AIDS-related KS or AIDS-KS) was described in homosexual and bisexual men, and was first reported as part of AIDS [90].

General Epidemiology

In developed countries, the introduction of ART has had a strong influence on the epidemiology of AIDS-KS. The incidence has decreased by up to 80% since its peak in the early AIDS epidemic because of improved control of HIV viremia and preserved CD4 counts and immune function [25]. Before the ART era, HHV-8/HIV-coinfected patients were estimated to be 400–2000 times more likely to develop KS than those with solely HHV-8 infection [25]. Since the introduction of ART, the incidence of KS in HIV-infected persons has diminished in the Western world. It is estimated that AIDS-KS in the United States has decreased by 10% per year from 1990 to 1997; by contrast, the prevalence of KS remains high among Africans, particularly in children [118]. The reasons for this changing epidemiologic trend in different parts of the world remain unclear, although it may be related to incomplete access to ART in resource-limited settings, contrasting with high access to ART in developed countries [118]. Further decreases after 2000 have been more modest, and AIDS-KS remains the second most common tumor arising in HIV-infected persons in the United States [25]. Currently there are four epidemiologic subtypes of KS (Box 41.12).

Box 41.12 Clinical-Epidemiologic Forms of Kaposi Sarcoma

- *Classic KS*: It occurs mainly in elderly men (male/female-ratio 10–15:1) of Mediterranean, Eastern European, or Jewish Ashkenazi origin, with a peak incidence after the 6th decade of life. Usually the lesions are confined to the lower limbs, and it is a slow-progressing disease, patients living 10 or more years after being diagnosed.
- *AIDS-KS*: It is considered an AIDS-defining illness and has a more aggressive behavior compared with the classic form. It usually arises in HIV-infected patients with low CD4 counts. Clinically, AIDS-KS lesions may be more widespread, often involving the face, trunk, lymph nodes, oral mucosa, and visceral organs. It affects mainly MSM and intravenous drug users aged 20–50 years.
- *Endemic (African) KS*: It occurs in people living in all parts of equatorial Africa, particularly in sub-Saharan Africa, mainly middle-aged black adults and children.
- *Iatrogenic or transplant-related KS*: It is described in iatrogenic immunosuppressed organ transplant recipients and patients receiving chronic immunosuppressive therapy (e.g., long-term corticosteroid therapy, cyclosporine, azathioprine, and other biological therapies). This KS form appears about 16 months after transplantation and frequently clears after discontinuation of immunosuppressive therapy. The incidence of KS is 400–500 times higher among organ transplant recipients than in the general population.

Bhutani et al. [25], Curtiss et al. [64], Hengge et al. [118], Radu and Pantanowitz [245]

Etiopathogenesis

HHV-8 is an essential factor in the pathogenesis of any KS type. Like other herpesviruses, HHV-8 establishes a latent infection in KS-spindle cells, eventually undergoing lytic replication, and several latent and lytic viral genes may play a role in its pathogenesis [25, 26, 245]. The lytic gene products seem important for the inflammatory and angiogenic component of KS lesions [119]. According to current knowledge, only individuals with specific conditions of immunodysregulation develop KS. HIV-infected cells produce several inflammatory and growth-promoting cytokines that potentiate HHV-8 activation, leading to increased viral load, antibody titers, and an expanded cell tropism that precedes the clinical appearance of AIDS-KS [119, 295].

Clinical Presentation

KS has a highly variable clinical course ranging from very indolent forms to a rapidly progressive disease. KS lesions typically involve the skin and/or mucosal surfaces (Fig. 41.59), at any location, but are typically concentrated in the lower extremities and the head and neck, in a symmetric linear distribution along tension skin lines [14]. KS presents as purplish, reddish blue, or dark brown/black lesions that evolve from early (patch stage) macules into plaques (plaque stage), which may subsequently develop into larger nodules (tumor stage) (Fig. 41.59). Different stages can coexist in the same individual at the same time. The tumors may easily bleed and ulcerate, may cause pronounced lymphedema (Fig. 41.59), and may invade subjacent tissues [25, 245]. Extracutaneous KS may affect lymph nodes and visceral organs, mainly the gastrointestinal and the respiratory tracts.

Complementary Examinations

The presumptive diagnosis is made based on the clinical history and physical examination, although biopsy is required for definitive diagnosis. Even in resource-limited settings, histologic confirmation is strongly encouraged [8, 321]. The histopathologic aspects are similar for KS subtypes; nevertheless, some studies have documented minor histopathologic differences between AIDS-KS and non-HIV-associated KS cases [245]. The characteristic histologic findings are angiogenesis, inflammation, and proliferation. The lesions usually present two main abnormalities, which are spindle-shaped cells arranged in a snail-like form with leukocyte infiltration and neovascularization [14]. Immunohistochemistry techniques may be useful to confirm the diagnosis and demonstrate endothelial cell markers (CD31, CD34, and factor VIII) as well as markers for lymphatic endothelial cells. Moreover, HHV-8 identification within KS lesion cells by using LNA-1 is the most diagnostically helpful immunostaining technique available to differentiate KS from its mimics [245]. Evaluation of patients with AIDS-KS must include a complete physical examination as well as a detailed checkup of the oral cavity, anogenital region, and lymph nodes, and also a rectal examination. Assessment of visceral involvement is suitable for patients with systemic symptoms, lymphadenopathy, or B-symptoms (unexplained fever, night sweats, >10% involuntary weight loss, or diarrhea persisting more than 2 weeks), occult blood in the stool, or unexplained iron-deficiency anemia [25, 321].

Therapeutic Approach

The treatment decision for AIDS-KS must consider the extent and the rate of tumor growth, patients' symptoms, lesion distribution and evolution pattern, immune status, and concurrent HIV-related complications. Several different therapeutic options are available. Currently there are no standard therapy protocols, the consensus is that all patients should receive ART, regardless of CD4 count [14, 174]. Major treatment goals are symptom palliation, prevention of disease progression, and improved quality of life [14, 25]. ART including protease inhibitors may represent the first treatment step for slowly progressive disease. There are cur-

Fig. 41.59 Kaposi's sarcoma. (**a**) Purplish plaques on the feet; (**b**) dark brown nodules, tumors, and marked lymphedema; (**c**) KS lesion on the palate; (**d**) violaceous patches in early-stage KS on the glans penis; (**e**) purplish plaques on the trunk; (**f**) detail of the typical KS lesion at the plaque stage on the forearm

rently no standardized or universally accepted criteria to guide which HIV-infected patients with KS would benefit most from concomitant chemotherapy in addition to receiving ART [321]. Inhibition of HIV replication, amelioration of the immune response against HHV-8, and perhaps some direct antiangiogenic activity of PI are beneficial effects of ART on AIDS-KS. Localized, symptomatic lesions may be treated with local approaches, such as intralesional chemotherapy, liquid nitrogen, laser therapy, localized radiotherapy, or surgical resection. Systemic chemotherapy is applicable for HIV patients not responding to ART and/or with widespread, symptomatic, rapidly progressive, life-threatening AIDS-KS with visceral involvement, and in IRIS-associated flares [25, 146, 174]. Chemotherapy treatment regimens commonly used in high-resource settings are single-agent liposomal anthracyclines (doxorubicin and daunorubicin) and single-agent paclitaxel. Other options, which are more widely used in lower-resource settings, include combination chemotherapy with vincristine, with or without nonliposomal doxorubicin [321].

Glossary

Antigenemia The condition of having an antigen present in the blood.

Cantharidin An odorless, colorless terpenoid secreted by many species of blister beetles, including broadly in genus *Epicauta*, and in species *Lytta vesicatoria* (Spanish fly). Externally, cantharidin is a potent vesicant (blistering agent), exposure to which can cause severe chemical burns.

Dermoscopy A noninvasive method that allows the in vivo evaluation of colors and microstructures of the epidermis, the dermoepidermal junction, and the papillary dermis not visible to the naked eye. These structures are specifically correlated to histologic features.

Dimorphic fungus Fungi that exist either in yeast form or as mold (mycelial form) depending on environmental conditions, physiologic conditions of the fungus, or genetic characteristics.

Gomori methenamine silver Used widely as a screen for fungal organisms and particularly useful in staining carbohydrates. It can be used to identify the yeast-like fungus *Pneumocystis jiroveci*, which causes a form of pneumonia called pneumocystis pneumonia (PCP) or pneumocystosis.

GUD (genital ulcer disease) Located on the genital area, usually caused by a sexually transmitted disease (STD) such as genital herpes, syphilis, chancroid, or chlamydia trachomatis. Genital ulcers are not strictly a sign of an STD.

Immune reconstitution syndrome (IRIS) Some people who start antiretroviral therapy (ART) encounter health problems even though their HIV comes under control. An infection that they previously had might return. In other cases, they develop a new disease. This is linked to improvements in the patients' immune systems. The problems usually occur in the first 2 months after starting HIV therapy. It may occur in about 20% of people starting ART.

LNA-1 (latent nuclear antigen) A Kaposi's sarcoma (KS)-associated herpesvirus (KSHV) latent protein initially found by Moore and colleagues as a speckled nuclear antigen present in primary effusion lymphoma cells that reacts with antibodies from patients with KS. LNA-1 has been suspected of playing a crucial role in modulating viral and cellular gene expression. It is commonly used as an antigen in blood tests to detect antibodies in persons that have been exposed to KSHV.

Majocchi's granuloma Can be defined as a deep folliculitis due to a cutaneous dermatophyte infection.

Meglumine antimoniate (MG) A medication used for treating leishmaniasis. It is manufactured by Aventis and sold as Glucantime in France and Brazil, and Glucantim in Italy. It belongs to a group of compounds known as the pentavalent antimonials. It is administered by intramuscular injection.

p24 antigen test Detects the presence of the p24 protein of HIV (also known as CA), the capsid protein of the virus.

PCR techniques Techniques used in molecular biology to amplify a single copy or a few cop-

ies of a piece of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence.

Periodic acid-Schiff (PAS) A staining method used to detect polysaccharides such as glycogen, and mucosubstances such as glycoproteins, glycolipids, and mucins in tissues.

Phlebotomine sandflies A subfamily of the family Psychodidae. In several countries, their common name is sand fly. The Phlebotominae include many genera of blood-feeding (hematophagous) flies, including the primary vectors of leishmaniasis and others.

Podophyllotoxin A nonalkaloid toxin lignan extracted from the roots and rhizomes of podophyllum species. it is used on the skin as a topical treatment of external genital warts, caused by some types of the human papillomavirus (HPV), and other warts.

Sodium stibogluconate (SSG) A medication used to treat leishmaniasis, only available for administration by injection. It belongs to the class of drugs known as the pentavalent antimonials, because they contain antimony in its oxidation state of 5. SSG is marketed under the name Pentostam, and is exceedingly phlebotoxic.

Superantigens A class of antigens that cause nonspecific activation of T cells resulting in polyclonal T-cell activation and massive cytokine release. They are produced by some pathogenic viruses and bacteria, most likely as a defense mechanism against the immune system.

Warthin–Starry stain A silver nitrate-based staining method (silver stain) used in histology. Warthin–Starry stains organisms dark brown to black, and the background light golden brown/golden yellow. This technique involves the argyrophilic reaction.

WHO (World Health Organization) A specialized agency of the United Nations concerned with international public health. It was established on 7 April 1948 and is headquartered in Geneva, Switzerland. The WHO is a member of the United Nations Development Group.

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Suggested Reading and Consulting

CDC Sexually Transmitted Diseases Treatment Guidelines 2015. Available at https://www.cdc.gov/std/tg2015/. Although the guidelines emphasize treatment, prevention strategies and diagnostic recommendations also are discussed. This comprehensive document can be the go-to reference for anyone who manages patients at risk for STDs.

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Guidelines on the Treatment of Skin and Oral HIV-Associated Conditions in Children and Adults. Geneva: World Health Organization; 2014. Available at http://www.who.int/maternal_child_adolescent/documents/skin-mucosal-and-hiv/en/These guidelines provide a summary of the key evidence and practice recommendations on the diagnosis and treatment of the main skin and oral conditions in HIV-infected adults and children. The primary audience for these guidelines is health professionals who are responsible for providing care to children, adolescents and adults in settings with HIV, primarily where resources are limited.

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HIV InSite. Available at http://hivinsite.ucsf.edu. Comprehensive, up-to-date information on HIV/AIDS treatment and prevention from the University of California San Francisco, USA.

Liverpool HIV Drug Interactions website. Available at http://www.hiv-druginteractions.org/. A comprehensive, user-friendly, free drug interaction charts. It provides clinically useful, reliable, up-to date, evidence-based information, freely available to healthcare workers, patients and researchers.

Unemo M, Ballard R, Ison C, Lewis D, Ndowa F, Peeling R. Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus. Geneva: World Health Organization (WHO); 2013. p. 107–29. Available at http://www.who.int/reproductivehealth/publications/rtis/9789241505840/en/. This manual provides a basic understanding of the principles of laboratory tests in the context of screening and diagnostic approaches, as well as antimicrobial susceptibility testing, as components of STI control. It covers each disease in a separate chapter providing detailed information on specimen collection, transport, and laboratory testing.

Human T-Cell Lymphotropic Virus Type-1 (HTLV-1) Infection in Dermatology

42

Achiléa Lisboa Bittencourt

Key Points

- Brazil is considered the largest endemic area for HTLV-1 and associated diseases. Notwithstanding, the actual prevalence of this infection in Brazil is not yet available
- Nowadays, with the safe sex campaigns to prevent HIV infection and screening of blood donors for HTLV-1/2, breastfeeding constitutes the principal means of HTLV-1 transmission
- ATL and infective dermatitis generally occur in carriers infected vertically. Notwithstanding, in Brazil there is no public health program to prevent transmission through breastfeeding
- HTLV-1 carriers are more susceptible to scabies, strongyloidiasis, superficial mycoses, bacterial skin diseases, and pulmonary tuberculosis than noninfected individuals
- Knowledge of ATL is very important for dermatologists because it affects the skin in a frequency varying from 43% to 72% as a primary or secondary condition.
- The literature on primary cutaneous ATL is very confusing, with different criteria, and for this reason this matter requires standardization
- Most cases of ATL are similar to mycosis fungoides clinically and histologically
- It is mandatory in endemic areas to search for HTLV-1 infection in all cases diagnosed as mature T-cell leukemia/lymphoma even in childhood and puberty.

Human T-Cell Lymphotropic Virus Type (HTLV-1)

Introduction

The human T-cell lymphotropic virus (HTLV-1) is a retrovirus isolated in 1980 from cells of a cutaneous T-cell lymphoma from a patient with adult T-cell leukemia/lymphoma (ATL). Soon after, a second human retrovirus was described, HTLV-2 [1]. Both are retroviruses that infect T lymphocytes and are similar in approximately 70% of their genome sequences; for this reason serologic cross-reactions exist between them [1].

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Although the majority of HTLV-1-infected persons remain asymptomatic carriers, HTLV-1 is associated with many diseases, whereas HTLV-2 is only sporadically associated with neurologic conditions [2]. In 2005 two other related viruses, HTLV-3 and HTLV-4, were described in Central Africa, but to date they have not been linked to human diseases [1].

Epidemiology

Four major geographic subtypes (genotypes) of HTLV-1 have been described: the Cosmopolitan subtype A, the Central African subtype B, the Central African/Pygmies subtype D, and the Australo-Melanesian subtype C. The Cosmopolitan subtype A, which comprises several geographic subgroups, is the most widespread. Until now these subtypes have not been related to the development of diseases [3].

It is estimated that HTLV-1 infects 5–10 million individuals worldwide, with data based on only infected individuals from known endemic areas from available and reliable epidemiologic studies. The actual number of infected people may be much higher because there are regions where epidemiologic data are not yet available. The main HTLV-1 endemic areas are the Southwestern part of Japan, sub-Saharan Africa, South America, the Caribbean area, and foci in Middle East and Australo-Melanesia [3].

Brazil is considered as the largest endemic area for HTLV-1 and associated diseases. Notwithstanding, the real prevalence of this infection in Brazil is not yet available. Most prevalence studies have been performed among pregnant women or blood donors, without discriminating between the viral types 1 and 2, revealing among pregnant women frequencies varying from 0.1% to 0.2% [3]. Among blood donors from 27 Brazilian capitals, from January 1995 to December 2000 prevalence rates were found to range from 0.4/1,000 in Florianopolis to 10.0/1,000 in São Luis [4] (Fig. 42.1).

A study of 6,754 pregnant women with discrimination between HTLV-1 and HTLV-2, in Salvador, Brazil, found that 0.84% were HTLV-1 carriers [5]. Four years later, in a city near Salvador, a similar frequency (0.98%) was found among 408 HTLV-1-infected pregnant women [6]. More recently, in Southern Bahia, a prevalence of 1.05% of HTLV-1 infection was found among 2,766 pregnant women [7]. A seroprevalence study of HTLV-1 infection among 5,842 blood donors was performed in five state capitals of four regions of Brazil, with results varying from 1.35% to 0.08%. The lowest seroprevalence was found in Florianópolis and Manaus and the highest in Salvador [8]. In this same city, in 2003 a population-based evaluation revealed an overall prevalence of infection of 1.76%. According to this study, infection rates were 2.0% for females and 1.2% for males, and the infection was more prevalent in individuals 51 years of age or older (8.4%) [9].

The transmission of HTLV-1 infection is generally cell associated because this virus is poorly infectious as cell-free particles. It is transmitted in three ways: vertically, from carrier mothers to their children (mainly through breastfeeding); through sexual contact; and parenterally (through blood transfusion or needle sharing among drug users) [10]. Intravenous exposure to contaminated blood is considered the most efficient way of HTLV-1 transmission [1]. Notwithstanding, the screening of blood donors to HTLV-1/2 has been mandatory in Brazil since 1993 [4]. Plasma and industrial blood products (albumin, immunoglobulin, and antihemophilic factors) do not transmit HTLV-1, but transmission occurs through packed red cells and platelets with frequency varying according to the period of storage, being of more risk in the first 14 days [1]. Sexual transmission is considered to occur mainly from males to females. The rate of HTLV-1 transmission from infected males to females is considered to be 60.8%, whereas transmission from infected females to males occurs only rarely (rate of 0.4%) [10].

Serologic surveys of children born to carrier mothers found carrier state rates varying from 15.4% to 25%. The viral transmission rate depends on HTLV-1 proviral load, duration of breastfeeding, and maternal–fetal concordant

Fig. 42.1 HTLV-1/2 serologic enzyme immunoassay (EIA) screening prevalence rates (per 1,000 donations) in blood donors from the capital cities of 26 states and the Federal District of Brazil (Reprinted from [4] by courtesy of Cadernos de Saúde Pública)

human leukocyte antigen (HLA) class I type [10, 11]. However, bottle-fed children may also become vertically infected. In these children the most probable routes of infection are transplacental or contamination in the birth canal [10]. Transmission via human milk is almost always vertical but may occur by means of breastfeeding by wet-nurses or by cross-nursing (horizontal transmission) [10, 12]. Cross-nursing is a relatively common habit among the poor in Brazil [12].In Brazil there is no public health program to prevent transmission through breastfeeding [13]. Nowadays, with safe-sex campaigns to prevent HIV infection and the screening of blood donors for HTLV-1/2, breastfeeding constitutes the principal means of transmission.

Pathogenicity

HTLV-1 is a complex retrovirus with a single-stranded diploid RNA genome that encodes structural and regulatory proteins and enzymes necessary for the viral replicative cycle [14]. The structural *gag*, *pr*, *pol*, and *env* genes are flanked by 5′ and 3′ long terminal repeats (LTRs). The pX region, situated between *env* and the 3′ LTR, includes regulatory genes encoding Tax, Rex, p21, p12, p13, and p30 proteins as well as the antisense gene encoding the HTLV-1 basic leucine zipper (HBZ) [15, 16] (Fig. 42.2). HTLV-1 protein expression in the infected cells promotes cell cycle progression and survival, and propagation of the proviral DNA by cell division [14].

Fig. 42.2 The HTLV-1 proviral genome. The gag, pr, pol, and env genes are flanked by 5′ and 3′ long terminal repeats (LTRs). In the 3′ portion of the genome is the pX region which includes regulatory genes encoding Tax, Rex, p21, p12, p13, and p30 proteins as well as the antisense gene encoding HTLV-1 basic leucine zipper factor (HBZ) (Modified from Matsuoka and Jeang [15]. Reprinted by courtesy of *Nature Reviews Cancer*)
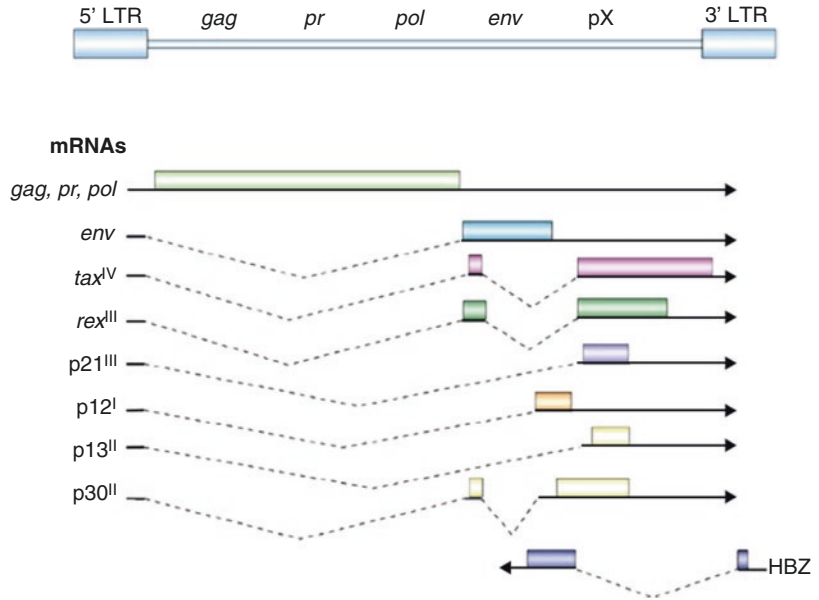
HTLV-1 infect different cells, such as T cells, B cells, fibroblasts, dendritic cells, and macrophages, but the virus persists predominantly in memory CD4$^+$ T cells [14]. The viral propagation occurs through various processes, including the virologic synapse and mitotic clonal proliferation of infected lymphocytes both stimulated by the virus. In the first process the contact between an infected and a target cell induces the formation of a microtubule organizing center through which the viral genome enters the uninfected cell [15] (Fig. 42.3). Within new infected cells, the single-stranded RNA virus is converted to proviral DNA and then integrated into host DNA by viral integrase [11]. Proviral integration in the genome is not random as previously supposed but occurs at different sites, called unique integration sites. In the second mechanism, the HTLV-1 stimulates infected T cells to proliferate by persistent or intermittent expression of Tax and HBZ, resulting in long-lived and abundant clones of infected cells in the circulation, each clone identified by a unique site of integration of the HTLV-1 provirus [16] (Fig. 42.4). As the majority of infected cells harbor only one copy of the provirus, the provirus load indicates the percentage of HTLV-1 infected cells among the circulating host lymphocytes [11].

Clonal proliferation of HTLV-1 infected cells is detected by Southern blot, inverse polymerase chain reaction (PCR), or inverse-long PCR [17]. In Fig. 42.5, a monoclonal pattern of an ATL case detected by inverse-long PCR is shown, determining without doubt the relation between the lymphoma and the virus. Cellular clonality is generally considered qualitatively as polyclonal (Fig. 42.4), oligoclonal, or monoclonal. Clonality of one HTLV-1 infected T-cell population represents the number of distinct clones and the abundance (size) of each clone. Recently, Gillet et al. [18] developed a new method to evaluate clonality which maps and quantifies a great number of HTLV-1 proviral insertion sites. These authors also defined the oligoclonality index to quantify clonality, varying from 0 to 1. The oligoclonality index is low in asymptomatic carriers and patients with HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) but this index is significantly greater in ATL patients, in some cases close to 1 (1.0 indicates perfect monoclonality, i.e., all the detected infected cells in an individual presents viral integration at the same point of the genome). Monoclonality equal to 1 is not a real possibility because there are always other small clones. Monoclonality appears when one or two clones became very abundant and predominate over the others, resulting in a sharp rise
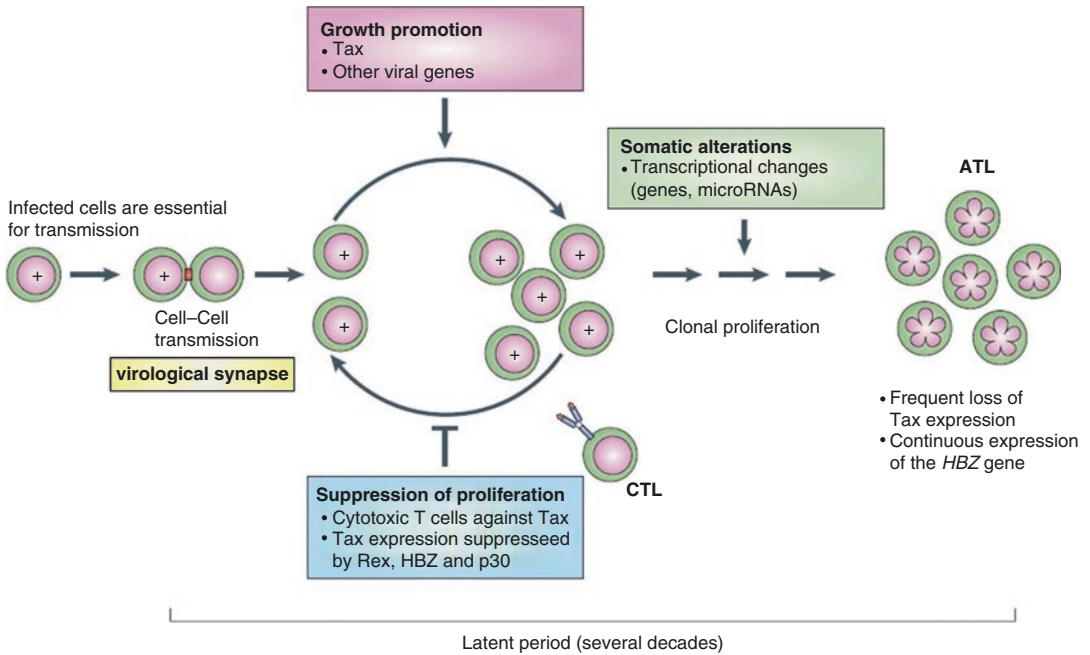
Fig. 42.3 Schematic model of the natural history of HTLV-1 infection to the onset of ATL. An uninfected T cell (empty nucleus) becomes infected (with a + in the nucleus) through a virologic synapse. After infection, HTLV-1 promotes clonal proliferation of infected cells by Tax and HTLV-1 accessory proteins. The proliferation of the infected cells is controlled by the action of the cytotoxic T cells (CTLs). During the latent period of many decades, genetic and epigenetic alterations accumulate in

the host genome and ATL may emerge in around 5% of the carriers. Tax expression is suppressed by Rex, HTLV-1 basic leucine zipper factor (HBZ), and p30, in order to escape from CTLs. Tax is needed early to initiate transformation but is not required later to maintain the transformed ATL cells. On the other hand, HBZ is important in all phases (Modified from Matsuoka and Jeang [15]. Reprinted by courtesy of *Nature Reviews Cancer*)
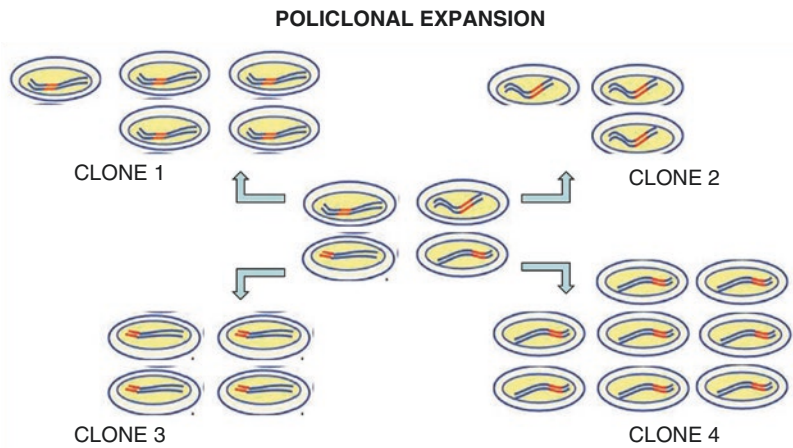
Fig. 42.4 A schematic representation of a polyclonal population. There are four different clones, each one with the same insertion point of the provirus and without great difference in size

in the oligoclonality index and culminating in ATL after a long period of time. An oligoclonality index of 0.48 for an asymptomatic carrier was observed while for ATL cases it varied from 0.79

to 0.85 [18]. This method is important for research, but the demonstration of clonality by Southern blot and inverse or inverse-long PCR (Fig. 42.5) continues to have real importance for

Fig. 42.5 Detection of monoclonal integration of HTLV-1 by inverse and long PCR. The PCR product shown in this figure was sequenced and contains human and virus DNA sequences. *Lane M* DNA molecular weight marker VIII (Roche), *lane P* patient with smoldering ATL (Courtesy of Dr. Lourdes Farré)

the differential diagnosis between ATL and other lymphomas not associated with HTLV-1.

HTLV-1 elicits abundant chronically activated CD8^{+} cytotoxic T lymphocytes (CTLs) [16]. The Tax protein is the main target of these cells, which destroy the host Tax-expressing cells, controlling infection. Notwithstanding, the virus may develop mechanisms to suppress Tax expression because loss of this expression constitutes advantage to the survival of infected cells through the escape from CTLs (Fig. 42.3) [15].

The proviral load depends on the efficiency of the CTL response [16]. It was demonstrated in Southern Japan that the high efficiency of the CTL response in HTLV-1 carriers is related to the host genotype in the HLA Class 1 and killer immunoglobulin-like receptor (KIR) loci, respectively HLA-A*02 and Cw*08, and KIRDL2 [16]. Besides this, there are reports about familial clustering of ATL, HAM/TSP, and infective dermatitis associated with HTLV-1 (IDH), indicating that host genetic background has real influence in the development of HTLV-1 related diseases [15, 19].

The increased number of infected cells in HTLV-1 infection causes an excess of immune reaction, leading to inflammatory diseases such as HAM/TSP, IDH, and HTLV-1-associated uveitis (HAU). HTLV-1-infected individuals with IDH or strongyloidiasis present a significantly increased proviral load and an alteration of HTLV-1 clonality attributable to higher average clone abundance (size) in relation to the asymptomatic carriers. These patients appear to be less capable of reducing clone abundance than HTLV-1 carriers without these associations. Both IDH and strongyloidiasis are considered to increase the risk of development of HTLV-1-associated diseases by the appearance of new clones and an increasing number of infected cells in the pre-existing HTLV-1^{+} clones [20].

The cytokine profile in HTLV-1 infection shows a pattern of a T-helper 1 (Th1) response. A spontaneous cytokine production is seen in asymptomatic carriers and in HAM/TSP and IDH patients with production of higher levels of interleukin (IL)-2, interferon (IFN)-γ, and tumor necrosis factor α (TNF-α) in these patients when compared with asymptomatic carriers. In addition, mononuclear cells from asymptomatic carriers produce high levels of the regulatory cytokines IL-5 and IL-10 when compared with seronegative individuals. The high IL-10 production in asymptomatic carriers downregulates the production of IFN-γ and may explain the asymptomatic status of these carriers, but in vitro such modulation is not seen in HAM/TSP patients [21, 22].

The similarities between the immunologic response in patients with IDH and HAM/TSP (an exaggerated Th1-type immune response) and the high proviral load observed in both diseases would appear to suggest that IDH constitutes a risk factor for the development of HAM/TSP [21]. Moreover, it has been observed that IDH may progress to HAM/TSP, even in childhood and puberty, a severe and disabling form of myelopathy that generally occurs in adulthood [12].

Considering that in ATL patients HTLV-1 infection generally occurs in childhood, a multistep carcinogenesis model has been proposed. Tax is considered to be the main inducer of the early stages of oncogenesis because it stimulates

cell proliferation and inhibits apoptosis of the infected cells. The proliferation of the infected cells after a prolonged period may result in the appearance of ATL in approximately 5% of HTLV-1 carriers (Fig. 42.3). There is some evidence that Tax is necessary to initiate transformation but is not required later to maintain the transformed phenotype of ATL cells. However, HBZ is continuously and durably expressed in ATL cells [15].

Host immune competence also plays an important role in controlling the proliferation of infected cells and avoiding leukemogenesis; thus, immunosuppression in HTLV-1-carriers may trigger ATL onset [15].

Diagnosis of Infection

Serology is the most commonly used method for the diagnosis of HTLV-1 infection. The specificity and sensitivity of the tests used to detect HTLV-1 antibodies have improved compared with previous versions. The most commonly used serologic screening test is the enzyme-linked immunosorbent assay (ELISA). Samples that repeatedly test positive in the ELISA must be retested in an immunoblot assay for serologic confirmation to distinguish between HTLV-1 and HTLV-2. For confirmation, the most commonly used method is the highly sensitive western blot 2.4, the specificity of which is 97.5% [17]. Cases that do not meet the criteria for HTLV-1 or HTLV-2 positivity are considered indeterminate. In these cases, molecular testing should be carried out, PCR being the most commonly used method. PCR performed directly on peripheral blood mononuclear cells is able to detect proviral DNA. As a result of its elevated sensitivity and specificity, this method is capable of clarifying indeterminate serologic status and even of detecting the infection in individuals who were defined as seronegative but who had a clinical status suggestive of HTLV-1-associated diseases. PCR is also a confirmatory test for HTLV-1 infection. However, most laboratories are unequipped to perform this method, which is also subject to failure if not performed carefully. PCR is also used to detect the virus in tumor tissue and in other biological specimens [17].

Considering that HTLV/HIV coinfection may have a prevalence of up to 10.9%, it is important to investigate this coinfection in HTLV-1 infected individuals. Besides, there is a suggestion in the literature that the HIV coinfection increases the risk of HAM/TSP [23].

HTLV-1-Related Diseases

HTLV-1 may cause various diseases such as ATL, HAM/TSP, IDH, and HAU, all of which are demonstrably related to the virus [24, 25]. IDH is a childhood disease whereas ATL, HAM/TSP, and HAU are considered adult diseases [26]. HTLV-1 infection has also been linked to polio-myositis, synovitis, thyroiditis, bronchoalveolar pneumonitis, and conjunctivitis sicca [24, 25]. Other conditions significantly more frequently seen among HTLV-1 carriers than in controls are xerostomy, periodontal disease, polyarthralgia, arthritis, erectile dysfunction, and overactive bladder [22]. In some carriers more than one HTLV-1 related disease may occur. In Brazil it has been observed that 14% of the ATL cases are associated with HAM/TSP [27]. Rarely, three HTLV-1-related diseases may appear in some patients simultaneously or sequentially [28, 29].

HTLV-1 acts slowly within the organism, hence the majority of the diseases caused by this virus are considered to be of late onset, emerging in adulthood even when the infection occurred in the early years of life [15]. Notwithstanding, besides IDH, other HTLV-1-related diseases may have a very early onset, occurring even in childhood [26].

HTLV-1 infection causes dysregulation of the immune system, which makes infected individuals more susceptible to other infections such as scabies, strongyloidiasis, superficial mycoses, bacterial skin diseases, and pulmonary tuberculosis in comparison with persons not infected with the virus [1, 17, 30].

In this chapter, only the diseases primarily affecting the skin or those which may cause cutaneous lesions are described.

Infective Dermatitis Associated with HTLV-1 (IDH)

IDH was described in detail as a new disease in 1966, in Jamaica, many years before the discovery of HTLV-1, as a severe form of chronic infected eczema occurring early in childhood [31]. In 1990, it was linked to this virus and in 1998 the criteria for its diagnosis were established [32, 33]. IDH has been reported to be more prevalent in female patients [12, 33].

Cases of IDH have been described, in order of frequency, in Jamaica, Brazil, South Africa, Peru, and Senegal. Isolated cases have been found in French Guyana, Colombia, Dominican Republic, and Chile [26]. In Japan, where the frequency of HTLV-I carriers is high, only three cases of IDH have been reported [34]. In Brazil, 43 reported cases were from Bahia [12, 35], 5 from Rio de Janeiro [36, 37], and 1 from Rio Grande do Sul [38]. It is possible that the majority of Brazilian cases of IDH were found in Bahia, because this is one of the most endemic regions for HTLV-1 in Brazil [4, 9]. In fact in this state there are projects designed to study IDH [12].

Clinical Aspects

This disease appears as a severe chronic eczema associated with a refractory, nonvirulent *Staphylococcus aureus* or β-hemolytic *Streptococcus* infection of skin and nasal vestibules. Its onset is usually under the form of rhinitis at around 18 months of age. IDH begins with an exudative eruption always involving the scalp and usually the external ear, neck, and retro-auricular areas (Figs. 42.6, 42.7, and 42.8). Table 42.1 shows the distribution of the lesions in 42 IDH cases [12]. In addition to the erythematous, scaly, and crusty lesions, pustules, scaly papules, follicular-like papules, and retro-auricular fissures are often found (Table 42.2) [12, 33]. Rhinorrhea and crusting in the nostrils (Fig. 42.9) are a common finding. Patients complain of pruritus, although it is not as intense as in atopic dermatitis. Blepharoconjunctivitis is found in the majority of cases [12].

Fig. 42.6 (**a**) Infective dermatitis associated with HTLV-1. Child with severe involvement of scalp with exudative and crusted yellow lesions. (**b**) Adherent yellowish crusts covering the scalp, and scaly and erythematous lesions in the retroauricular areas and neck. Note erosions on scalp

Fig. 42.7 Infective dermatitis associated with HTLV-1. Child with lesions on the neck and axillae. Note crusting of the nostrils

The mean age at onset of IDH is 2.6 ± 2.4 years (range, 2 months to 11 years) and the mean age at complete disappearance of disease is 15 years (range, 10–20 years), but infrequently it may persist until at least 23 years of age [12].

Fig. 42.8 Infective dermatitis associated with HTLV-1. Extensive involvement of genitalia and groins. In the low abdomen there are many follicular papules

Table 42.1 Distribution of lesions in 42 patients with infective dermatitis associated with the human T-cell lymphotropic virus type 1 [12]

Distribution of lesions	Patients, n (%)
Scalp	42 (100)
Retroauricular regions	42 (100)
Neck	37 (88.0)
Axillae	35 (83.3)
Groin	33 (78.6)
Paranasal skin	30 (71.4)
Ears	30 (71.4)
Thorax	27 (64.3)
Abdomen	26 (62.0)
Antecubital and popliteal fossae	24 (57.1)
Eyelids	24 (57.1)
Forehead	23 (54.8)
Perioral region	21 (50.0)
Umbilicus	17 (40.8)
Limbs	15 (35.7)
External genitalia	14 (33.3)
Buttocks	7 (16.6)

Table 42.2 Frequency of lesions in infective dermatitis associated with the human T-cell lymphotropic virus type 1 [12]

Distribution of lesions	Patients, n (%)
Erythematous-scaly-crusty lesions	42 (100)
Retroauricular fissures	32 (76.2)
Slightly erythematous-scaly papules	32 (76.1)
Crusting of nostrils	27 (64.3)
Fine papular rash	25 (59.5)
Blepharoconjunctivitis	24 (57.1)
Follicular papules	19 (45.2)

Fig. 42.9 Infective dermatitis associated with HTLV-1. Erythematous-scaly lesions on and around the nose and upper lip. There is crusting on the nostrils covered by yellow crusts

Table 42.3 Major criteria for diagnosis of infective dermatitis associated with the human T-cell lymphotropic virus [12, 17]

1. Presence of erythematous-scaly, exudative, and crusted lesions of the scalp, retroauricular areas, neck, axillae, groin, paranasal and perioral skin, ears, thorax, abdomen, and other sites
2. Crusting of nostrils and/or rhinorrhea
3. Chronic relapsing dermatitis with prompt response to appropriate therapy but prompt recurrence on discontinuation of treatment
4. Diagnosis of HTLV-1 infection (by serologic or molecular biological testing)

Modified from La Grenade et al. [33]
Of the four major criteria, three are required for diagnosis, with mandatory inclusion of 1, 3, and 4. To fulfill criterion 1, involvement of ≥3 of the sites is required, including involvement of the scalp and retroauricular areas
HTLV-1 human T-cell lymphotropic virus type 1

Diagnosis

In 2010, Bittencourt and Oliveira [17] proposed a modification in the main criteria established by La Grenade in 1998 [33] for the diagnosis of IDH. The modified criteria are listed in Table 42.3. According to La Grenade et al. [33] the areas affected in IDH are the scalp, axillae and groin, external ear and retro-auricular areas, eyelid margins, paranasal skin, and/or the neck; however, no reference was made to the frequency of the affected areas and which of the involved areas were essential for diagnosis. In 42 cases in Bahia, lesions were present on more areas of the body, being found on ≥3 areas in all cases. Furthermore, the scalp and retro-auricular areas were invari-

ably affected, and the lesions were disseminated in 83% of cases. Thus it was emphasized in the modified criteria that involvement of ≥3 of the sites is required, including involvement of the scalp and retro-auricular regions [12].

Crusting of the nostrils (Fig. 42.9) was absent in some patients, and sometimes appears only during subsequent relapses. Therefore, the presence of crusting of the nostrils cannot be considered an obligatory factor for the diagnosis of IDH, although it represents, when present, an important criterion for diagnosis. Because rhinorrhea is a common symptom in children in several other diseases, it should not constitute a criterion for diagnosis of IDH [17]. However, the relapsing nature of disease, not present in the original main criteria [33], is characteristic of IDH, so this aspect should be considered to be indispensable for diagnosis. On the other hand, the criterion requiring onset in early childhood should be removed, because the disease may begin later in childhood, as late as 11 years of age, or in adulthood [17]. On the other hand, it is important to consider not only the serologic diagnosis, which may fail (albeit infrequently), but also diagnosis of the infection by molecular biology. In seronegative patients with the classic characteristics of IDH, PCR for HTLV-1 must be performed in peripheral blood mononuclear cells to clarify the diagnosis [12].

Differential Diagnosis

The differential diagnosis of IDH should be made mainly with atopic and seborrheic dermatitis. Seropositivity for HTLV-1 is not the only criterion for the diagnosis of IDH; clinical criteria are also very important. In childhood atopic dermatitis occurring after 2 years of age, the lesions partially resemble those of IDH; however, in IDH the lesions are more exudative, infected, and exuberant, and nasal crusting is frequently found. The discovery of lesions in the antecubital and popliteal fossae may sometimes hamper the differential diagnosis with atopic dermatitis [12].

In seborrheic dermatitis, lesions are erythematous and scaling, and less infected than those found in IDH. On the other hand, rhinitis and a papular rash may be present, features that are not found in seborrheic dermatitis. Another very relevant difference is the presence of pruritus in IDH, which is practically nonexistent in seborrheic dermatitis. In seborrheic dermatitis, the squames are oily and *Pityrosporum* is often found. Moreover, IDH responds well to treatment with sulfamethoxazole/trimethoprim and antibiotics [12].

Infective Dermatitis in Adulthood

The onset of IDH may occur in adult life, characteristics in such cases being similar to those of the infantile-juvenile IDH (Fig. 42.10). In 2006, two cases of late-onset IDH were described in Bahia, Brazil, both in females, one of which was associated with HAM/TSP [39]. Later on, nine more cases were reported, seven of them in females and four associated with HAM/TSP [40–43].

Pathology

IDH cannot be diagnosed by histology. Microscopically, acanthosis, hyperkeratosis, and/or parakeratosis and crusting are found. Spongiosis is present in only 50% of cases. In some cases, obliteration of the basal layer and epidermotropism of lymphocytes are found, mimicking mycosis fungoides. In the dermis, a slight to moderate infiltration of typical lymphocytes is found, consisting predominantly of CD8+ T lymphocytes with no cytotoxic granulations [44].

According to the literature, CD4+ cells predominate in atopic dermatitis skin lesions; therefore, the finding of CD8+ cells in IDH may represent a distinguishing feature to enable differential diagnosis to be made between these two diseases [44].

Progression to HAM/TSP and ATL

Seventeen of 36 (47.2%) IDH patients followed-up in Bahia progressed to HAM/TSP, a severe

Fig. 42.10 Infective dermatitis associated with HTLV-1 initiated in adulthood. (**a**) Presence of erythematous and scaly lesions on the scalp and neck. (**b**) Another adult patient with retroauricular lesions and many erythematous papules on the posterior aspect of the neck

myelopathy that generally occurs in adulthood [12]. There have also been a few isolated reports on the progression of IDH to ATL [29, 35, 45, 46]. Thirty-seven per cent of ATL cases with skin involvement observed in Bahia reported a history of severe eczema in childhood very suggestive of IDH [47]. On the other hand, abnormal cells, including flower cells, were observed in 17% of a cohort of 30 IDH children and adolescents (Fig. 42.11) [48]. Moreover, proviral monoclonal integration investigated by inverse-long PCR was observed in seven of these IDH patients in whom viral and human DNA sequences were found. In these patients, the percentage of abnormal T cells or flower cells ranged from 2% to 3% and they were not considered as smoldering ATL because they did not have lymphoma or ≥5% of atypical cells in peripheral blood. On the other hand, all of them presented T-cell polyclonality [49]. The pres-
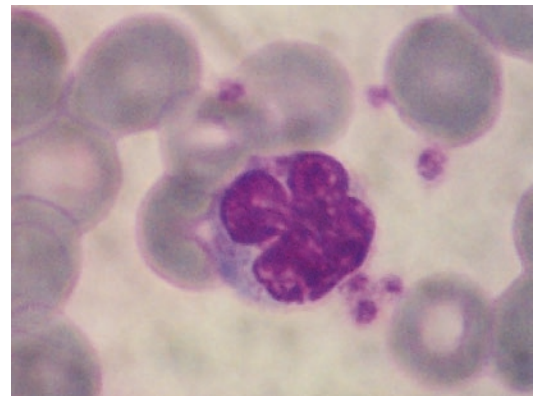
Fig. 42.11 Peripheral blood smear with a flower cell (lymphocyte with condensed chromatin and marked multilobulated nucleus) (Wright stain, ×1,000)

ence of proviral integration without disease is considered a pre-ATL condition [50]. These data may suggest that IDH constitutes a risk factor for the development of ATL.

Treatment

Since IDH is always associated with bacterial infection, it responds well to a combination of trimethoprim/sulfamethoxazole; however, the disease recurs whenever the medication is discontinued. Antihistamine drugs, topical corticosteroids, and emollients are also recommended [12].

Adult T-Cell Leukemia/Lymphoma (ATL)

Knowledge of ATL is very important for dermatologists because it affects the skin in a frequency varying from 43% to 72%, as a primary or secondary condition [17]. In Bahia, Brazil, among cases of primary cutaneous T-cell lymphoma, 26.4% correspond to primary ATL. This result is closer to that found in Lima, Peru, where 19.4% of primary cutaneous T-cell lymphomas were primary cutaneous ATL [51]. These data show that this is a frequent problem in these regions.

ATL is considered as a disease with dismal prognosis and poor response to chemotherapy; however, there are cases with longer survival [52, 53]. ATL is generally reported in adults, the mean age at onset being around 57 years in Japan [54], 49 years in Brazil [27], and 43 years in Jamaica [55]. However, in rare cases onset may be earlier, even in childhood [26].

Classification, Clinical Features, and Diagnosis

ATL has been classified into four types, namely acute, chronic, lymphoma, and smoldering [54]. In 2007, Bittencourt et al. [27] proposed the inclusion in this classification of another clinical type, the primary cutaneous tumoral (PCT). This classification is based on the presence or absence of lymphocytosis and hypercalcemia, percentage of abnormal lymphocytes, levels of lactic dehydrogenase (LDH), sites of involvement, and morphology of skin lesions. These types differ in their presentation, progression, and response to treatment [54, 56]. The characteristics of each type of ATL are summarized in Table 42.4.

The chronic type has been subtyped into favorable and unfavorable, the latter presenting high LDH, high blood urea nitrogen, and/or low albumin levels and a worse prognosis in relation to the favorable subtype [56].

When the patient presents ≥5% of abnormal cells in peripheral blood smoldering, ATL is considered as leukemic [54, 56]. Leukemic smoldering ATL may appear with or without skin or lung involvement (Table 42.4) [57, 58]. When asymptomatic these patients are generally diagnosed by chance during a regular health checkup [58]. Notwithstanding, to recognize these asymptomatic leukemic smoldering

Table 42.4 Clinical classification of adult T-cell leukemia/lymphoma (ATL) modified from the Shimoyama classification [17, 27, 54]

ATL CLINICAL FORMS	Lymphocytosis	Abnormal lymphocytes	LDH levels	Hypercalcemia	Involvement of organs
Smoldering					
1. Primary cutaneous	Absent	<5%	≤1.5 × N	Absent	Only Skin
2. Nonleukemic	Absent	<5%	≤1.5 × N	Absent	Skin and lung or only lung
3. Leukemic	Absent	≥5%	≤1.5 × N	Absent	Skin and/or lung
4. Leukemic	Absent	≥5%	≤1.5 × N	Absent	Without involvement
PCT	Absent	<5	≤1.5 × N	Absent	Skin
Chronic #	Present	Present	≤2 × N	Absent	Any organ except bone, GIT and CNS
Lymphoma	Absent	≤1	Variable	May occur	Lymph node[a] and any other organ
Acute	Usually present	≥5rgg	>1.5 × N	May occur	Any organ

#Subtyped into favorable and unfavorable according to the serum levels of albumin, urea nitrogen, and lactic dehydrogenase (*LDH*). *CNS* central nervous system, *GIT* gastrointestinal tract, *N* normal value, *PCT* Primary cutaneous tumoral
[a]Involvement of lymph node is a mandatory criterion

patients it is necessary to assess systematically abnormal cells in peripheral blood. There are rare references about the outcome of leukemic smoldering ATL in the literature [57, 58]. In one evaluation of 157 smoldering cases, without discrimination between leukemic and nonleukemic cases, 76% had skin lesions and only 2% presented lung involvement, indicating that skin involvement is much more frequent than pulmonary involvement in smoldering ATL [59].

The PCT type is similar to the nonleukemic smoldering type without pulmonary involvement, except for the presence of skin nodules and/or tumors and worse prognosis [47]. In Japan, the smoldering and chronic forms are considered indolent ATL and the PCT type is included within the smoldering ATL [58–62]. The more aggressive forms of ATL are acute, lymphoma, PCT, and unfavorable chronic, survival being longer in patients with the smoldering and favorable chronic types. The diverse forms of ATL may progress to more aggressive types [56].

Similarly to T-cell lymphomas unassociated with HTLV-1, ATL appears on the skin as primary or secondary. Cutaneous lesions appear as patches, plaques, multiple papules, nodules, tumors, diffuse infiltration, and erythroderma (Figs. 42.12 and 42.13a–c) [47]. The lesions are always multiple and are diffuse in 50% of cases [47]. Rarely, purpuric lesions (Fig. 42.13d), vesicles (Fig. 42.14), or bullae are observed [63–65]. Sawada et al. [66], evaluating 119 ATL patients in Japan, observed the following frequency of skin lesions: nodulotumoral (38.7%), plaques (26.9%), multipapular (19.3%), patches (6.7%), erythrodermic (4.2%), and purpuric (4.2%). All of these erythrodermic patients had acute ATL. In Bahia, Brazil, among 80 ATL cases the frequency of the different types of skin lesions were erythroderma (30%), patch/plaque (28.7%), nodulotumoral (22.5%), multipapular (16.25%), and purpuric (2.5%). Erythroderma was observed in all types of ATL, but more frequently in the smoldering and acute types (unpublished data).

The criteria for the diagnosis of ATL are: (1) positive HTLV-1 serology; (2) cytologic or histopathologic finding of leukemia or T-cell lymphoma CD4+/CD25+; (3) presence of abnormal T

Fig. 42.12 Primary cutaneous smoldering ATL with erythroderma

lymphocytes in blood smears; and (4) demonstration of monoclonal HTLV-1 proviral integration whenever possible [56]. Table 42.5 summarizes the routine for evaluation of ATL patients at diagnosis [56, 67].

The abnormal lymphocytes found in the ATL patients in peripheral blood may consist of several types including flower cells, which are cells with marked polylobulated nuclei containing condensed chromatin [68]. Flower cells, generally found in acute ATL and occasionally in the chronic and smoldering types, are considered to be pathognomonic of ATL [54, 56]. The presence of these cells is important because it represents a fast and simple way of diagnosing ATL using a Giemsa- or Wright-stained blood smear [69].

In cases of doubtful diagnosis, ATL can be differentiated from other T-cell lymphomas unassociated with HTLV-1 but occurring coincidentally in infected individuals through the HTLV-1 proviral integration analysis (Fig. 42.5). However, this analysis is not essential in the diagnosis of most cases [70]. Its importance as scientific evi-
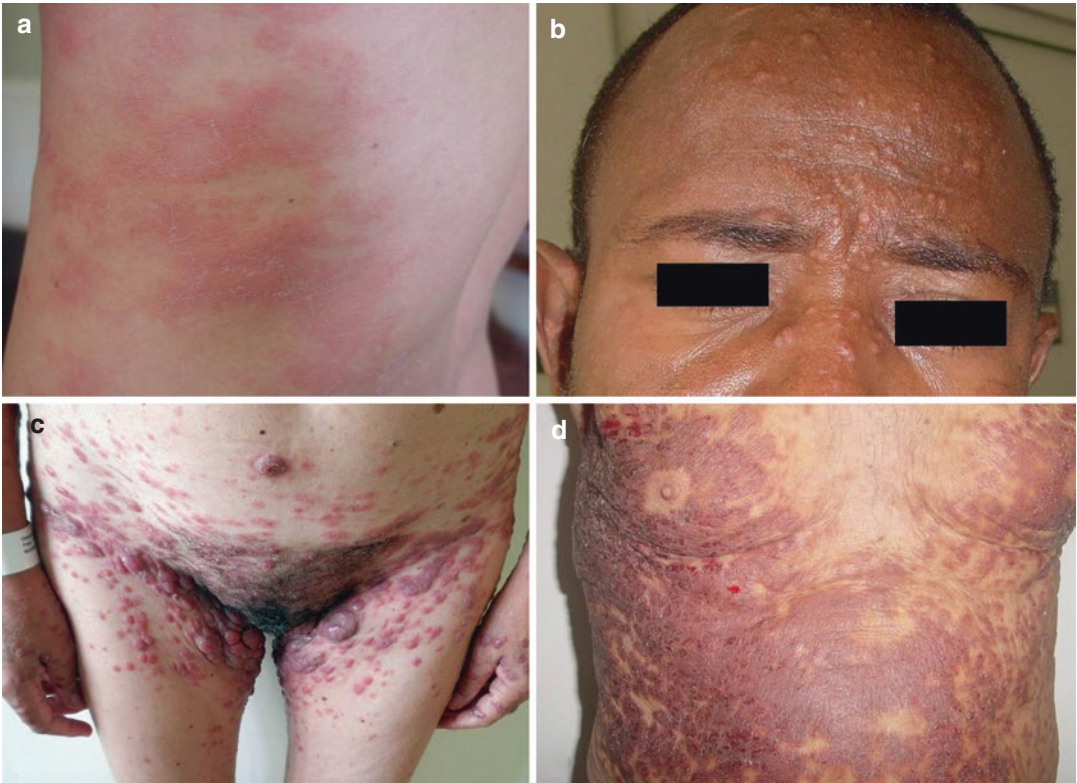
Fig. 42.13 (**a**) Favorable chronic ATL patient with erythematous infiltrated plaques. (**b**) Acute ATL patient with multipapular lesions and few nodules on the face. (**c**) Primary cutaneous tumoral ATL with disseminated nodules and tumors on the skin but without lymphocytosis and systemic involvement. (**d**) Diffuse purpuric lesion with areas of erosion in an acute ATL patient

Fig. 42.14 Chronic ATL with vesicles mimicking dyshidrosis on the palms of the hands

dence is higher in patients with atypical features, such as very long evolution or very early appearance [27]. On the other hand, it is known that in endemic areas only rare cases of T-cell lymphomas other than ATL have been observed developing in HTLV-1 carriers [56].

Primary Cutaneous Adult T-Cell Leukemia/Lymphoma

It is always important to evaluate whether skin involvement in lymphoma is primary or secondary, since clinical behavior and prognosis are quite different. Among 80 ATL cases with skin involvement, a statistically significant difference was observed between the median survival time of the primary cutaneous ATL in relation to the secondary (58 months versus 10 months for secondary ATL) (Fig. 42.15) (unpublished data).

It has been well established that the principal criterion for considering any type of lymphoma to be primary cutaneous is that it

Table 42.5 Examinations for evaluation of adult T-cell leukemia/lymphoma (ATL) patients at diagnosis [56, 67]

1. *Physical examination*
With full skin inspection and search for adenopathy and hepatosplenomegaly
2. *Laboratory examinations*
Confirmation of HTLV-1 serology (most laboratories in Brazil do not perform confirmation)
Complete blood counts
Blood smears for assessing abnormal lymphocytes including "flower cells"
Determination of serum
LDH (prognostic factor)
Albumin (prognostic factor of chronic ATL)
Urea nitrogen (prognostic factor of chronic ATL)
Calcium (to rule out hypercalcemia)
Soluble IL-2 (prognostic factor), when available
Stool parasitologic examination (Baerman) to rule out strongyloidiasis
Peripheral blood immunophenotyping (necessary to diagnose ATL in patients without histologically proven tumor)
3. *Imaging examinations*
Cervical, thoracic, abdominal, and pelvic CT (when impossible perform at least thoracic X-ray, also to rule out tuberculosis and abdominal and pelvic USG)
CT scan or MRI of the head (in cases with neurologic symptoms unrelated to HAM/TSP)
Skeletal X-ray in patients with hypercalcemia
4. *Cytologic and/or anatomopathologic examinations*
Cutaneous biopsy: histopathology with immunohistochemistry
Puncture or lymph node excision: cytology or histopathology with immunohistochemistry
5. *Useful behaviors in selected cases*
Pregnancy test in women of childbearing age
Endoscopy of the upper digestive tract (patients with digestive symptoms)
Lumbar puncture, in aggressive forms or in patients with neurologic symptoms unrelated to HAM/TSP
Myelogram or bone marrow biopsy (generally not required to make the diagnosis of ATL, but may be useful in the aggressive forms)
PET scan, when indicated and if there is availability
Transplantation evaluation, when indicated

CT computed tomography, *HAM/TSP* HTLV-1-associated myelopathy/tropical spastic paraparesis, *HTLV-1* human T-cell lymphotropic virus type 1, *IL-2* interleukin-2, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *USG* ultrasonography

be confined to the skin. Therefore, the smoldering nonleukemic type with no pulmonary involvement (primary cutaneous smoldering ATL) and the PCT type represent cases of primary cutaneous ATL (Table 42.4) [17, 47]. In brief, to consider a case of ATL to be primary cutaneous, there should be no lymphocytosis, no hypercalcemia, no extracutaneous involvement, with the LDH levels either slightly elevated or normal and fewer than 5% of abnormal cells found in peripheral blood. Besides, the patient must have a lymphomatous infiltration in the skin [47]. All smoldering ATL patients diagnosed in Bahia, Brazil, to date are nonleukemic smoldering ATL and only present skin involvement [17, 47]. Notwithstanding, the primary cutaneous ATL is not yet universally accepted because it is not included in the classifications of lymphoma defined by the World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC) [71, 72].

As the literature regarding primary cutaneous ATL is very confusing with different criteria, this matter requires standardization (Table 42.6) [27, 47, 57, 73–76]. Most authors continue to use the term cutaneous ATL without emphasizing the primary skin condition of this entity.

Amano et al. [74] detected a significantly higher proviral loading in the smoldering form (considered by these authors as leukemic) compared with the cutaneous ATL (nonleukemic smoldering), and considered that this difference could represent a means to distinguish between these two entities. Similarly, Yonekura et al. [57] found a higher proviral load in leukemic smoldering ATL with or without cutaneous lesions than in cutaneous ATL (nonleukemic smoldering). In fact, if cutaneous ATL has a lesser percentage of infected cells in peripheral blood (<5%), the proviral load must be lower than that of the leukemic subtype (≥5%). As already mentioned, the proviral load corresponds to the number of HTLV-1-infected cells in peripheral blood.

Given that the Shimoyama's classification [54] continues to be used and recommended in the literature [56], we believe that the PCT form should be added to this classification and that the
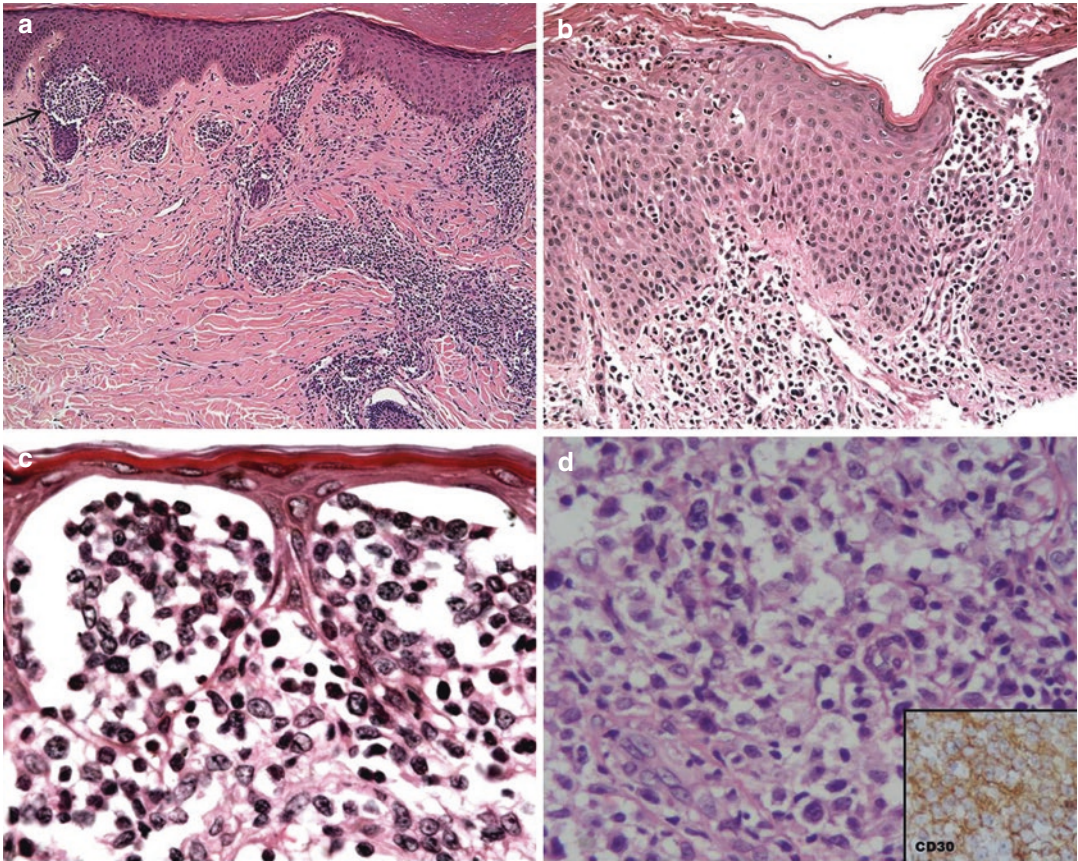
Fig. 42.15 Among 80 ATL cases with skin involvement, a statistically significant difference was observed between the median survival time of the primary cutaneous ATL and that of the secondary atl (58 months versus 10 months for secondary ATL) Oliveira PD, et al, 2016)

variant of the smoldering form that corresponds to primary cutaneous ATL without nodules and tumors should be defined as another type of smoldering ATL (Table 42.4) [17, 27, 47]. Whatever the nomenclature to be adopted in the future, it is important to separate the primary cutaneous tumoral ATL from the nontumoral form (primary cutaneous nonleukemic smoldering) because their prognosis is different and, therefore, the therapeutic approach should be different [17, 47].

One possible means of differentiation between ATL with erythematous papular and nodulotumoral lesions was suggested by Miyata et al. (2010) [75], in Japan, who found distinct genomic profiles in these two subtypes of primary cutaneous ATL. Notwithstanding, this issue should be investigated with a larger number of cases.

Histopathologic and Immunohistochemical Aspects of Skin Lesions

The morphologic appearance of ATL in skin sections is highly variable and often mimics established pathologic types of T-cell lymphomas unassociated with HTLV-1. The diagnosis of ATL can only be made following serologic or molecular evaluation since this T-cell lymphoma has no specific histologic characteristics. Unaware of the serologic findings, the pathologist generally classifies HTLV-1-associated lymphomas as peripheral T-cell lymphoma, unspecified (PTCL-U), mycosis fungoides (MF), or anaplastic large-cell lymphoma (ALCL) [27].

Table 42.6 Different criteria regarding primary cutaneous adult T-cell leukemia/lymphoma (ATL)

Authors	Designation	Subtyping or different cutaneous lesions	Criteria related to Shimoyama classification	Prognosis
Johno et al. (1992) [73][a]	Cutaneous ATL	(a) Erythematopapular	The same as for nonleukemic smoldering ATL	Tumoral with worse prognosis
		(b) Tumoral		
Bittencourt et al. (2007) [27]	Primary cutaneous ATL with two subtypes	1. Smoldering ATL (without nodulotumoral lesions)	1. Smoldering ATL	PCT with worse prognosis
		2. PCT ATL	2. PCT ATL to be added to the Shimoyama classification	
Amano et al. (2008) [74]	Cutaneous ATL	(a) Erythematopapular	1. The same as for nonleukemic smoldering ATL without lung involvement	–
	Smoldering ATL	(b) Tumoral	2. Leukemic without skin lesions	
Bittencourt et al. (2009, 2010) [17, 47]	Primary cutaneous ATL with two subtypes	1. Primary cutaneous smoldering ATL without nodulotumoral lesions	1. Nonleukemic smoldering ATL without lung lesions and nodulotumoral lesions (<5% of abnormal cells in PB)	PCT with worse prognosis
		2. Primary cutaneous tumoral (PCT) with nodulotumoral lesions	2. PCT: the same but with skin nodulotumoral lesions	
Miyata et al. (2010) [75]	Cutaneous type ATL	(a) Erythema/papule	Include leukemic and nonleukemic smoldering and two chronic types	–
		(b) Nodule/tumor		
Yonekura et al. (2015) [57]	Cutaneous type ATL	–	Include leukemic and nonleukemic smoldering	–
Tsukasaki et al. (2014) [76][b]	Extranodal primary cutaneous variant of lymphoma type ATL	–	Smoldering ATL with primary cutaneous lesions with poor prognosis and histology of high-grade lymphoma	Worse prognosis than smoldering without nodulotumoral lesions

PB peripheral blood, *PCT* primary cutaneous tumoral
[a]Without clearly defining the criteria for differentiation between cutaneous and smoldering adult T-cell leukemia/lymphoma (ATL)
[b]Among eight cases they included seven with nodulotumoral lesions and one with plaques

In cases in which morphology is similar to MF, the infiltrate consists of small, irregular cells frequently associated with epidermotropism of varied intensity, infiltrating the basal layer linearly, forming Pautrier abscesses (Fig. 42.16a) or setting up a pagetoid infiltration (Fig. 42.16b). PTCL-U is characterized by an infiltration of pleomorphic medium-sized to large cells, sometimes infiltrating the subcutaneous tissue. Epidermotropism of lymphocytes and Pautrier abscesses may be present (Fig. 42.16c). Angio- and folliculotropism can be observed less frequently. In ALCL, neoplastic cells are large and cohesive with abundant cytoplasm and anaplastic nuclei (Fig. 42.16d) [47].

In ATL, the immunophenotype most commonly observed is CD3+/CD4+/CD5+/CD7−/CD8−/CD20−, CD79a−, CD25+ [72]. However, in 52 cases with skin manifestations, 15 were CD8+ but no statistically significant difference was observed in median survival time between the groups of CD8+ and CD8− cases. In two cases with ALCL morphology, the phenotype was CD30+/ALK− [47]. It is always important to determine the proliferative index of ATL lesions, and this may be performed by immunohistochemistry for which most used marker is Ki-67. This evaluation is important since there is a negative correlation between the rate of the proliferative index and survival in ATL [27].
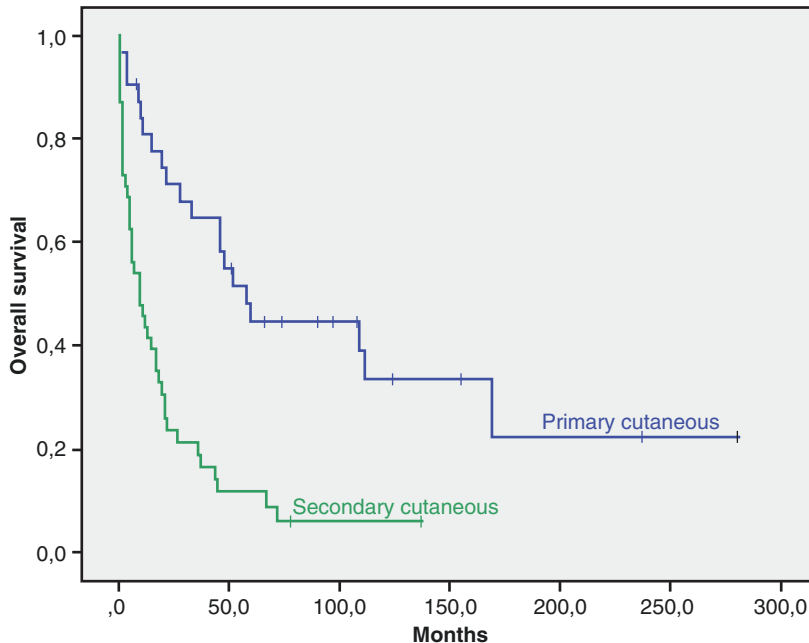
Fig. 42.16 (**a**) Mycosis fungoides pattern in a chronic ATL patient. Presence of small atypical lymphocytes in the upper and mid dermis and one Pautrier microabscess (*arrow*) (H&E, ×200). (**b**) Mycosis fungoides pattern in a primary cutaneous smoldering ATL patient. The atypical lymphocytes present in the dermis infiltrate the epidermis in a pagetoid pattern until the corneous layer (H&E, ×200). (**c**) Peripheral T-cell lymphoma of unspecified pat- tern in a patient with primary cutaneous tumoral ATL. Dermal infiltration of median and large anaplastic lymphocytes with epidermal atrophy and two large Pautrier abscesses (H&E, ×640). (**d**) Anaplastic large cell lymphoma pattern in a patient with primary cutaneous smoldering ATL. Large cells with abundant and eosino- philic cytoplasm and anaplastic nuclei (H&E, ×400). Inset: CD30⁺ cells (×200)

There was no difference in histopathology between the lesions that were primary and those that were secondary to the skin except for the frequency of histologic types, MF morphology being more common in primary cutaneous ATL while PTCL-U was more frequent in secondary cutaneous ATL [17]. In addition, ATL cases with MF morphology were more frequent in the smoldering and chronic forms and presented a proliferative index <18%, aspects that are indicative of a less aggressive outcome [47]. Most cases of ATL with cutaneous lesions resemble MF clinically and histologically [77, 78].

Histopathologic Differential Diagnosis

In the smoldering primary cutaneous form, the diagnosis of which is frequently based on the finding of a T-cell lymphoma with small and medium-sized cells at skin biopsy, histologic differential diagnosis may be hampered in view of cutaneous lymphoid hyperplasia that mimics lymphoma. In these cases, immunohistochemistry is not usually helpful and analysis of the rearrangement of the genes that codify the T-cell receptors in the skin lesions has to be performed to verify whether there is monoclonal expansion of the T lymphocytes, thus enabling differentiation to be made between these two entities [17]. It should be emphasized that HTLV-I infection in carriers or patients with HAM/TSP may lead to erythematous, inflammatory, noninfectious, and nonlymphomatous skin lesions, often with a histologic suspicion of malignancy [79, 80]. These cases must also be differentiated from cutaneous T-cell lymphomas. On the other hand, patients with HTLV-1 infection often have scabies, even crusted scabies, conditions that may appear histologically as a reactional lymphoid hyperplasia, which often mimics cutaneous T-cell lymphoma [81].

Except for the leukemic types of ATL, which are usually diagnosed by hematopathologists, the diagnosis of ATL is performed by pathologists in tissue biopsy specimens. Thus, it is important that in endemic areas for HTLV-1, these professionals be aware that ATL, besides manifesting histologically as PTCL-U, may also resemble MF or ALCL and that HTLV-I infection should be investigated in these T-cell lymphomas [27].

Prognosis

A study evaluating the type of skin lesions in relation to prognosis indicated that the erythrodermic, followed by the purpuric, nodulotumoral, and multipapular had the poorest prognoses with median survival time of 3.0, 4.4, 17.3, and 17.3 months, respectively. On the contrary, the patch and plaque lesions exhibited much better survival rates (188.4 versus 115.9 months, respectively) [66]. In our experience, the poorer prognosis was also observed in patients with purpuric and nodulotumoral lesions but patients with erythroderma had a median survival time a little better (17 months). However, our cases with erythroderma have also been observed in the smoldering ATL form with the best prognosis in Bahia, Brazil (unpublished data).

The prognosis of smoldering ATL with skin eruptions has been considered poorer than that without skin involvement [62]. Notwithstanding, the smoldering ATL with nodulotumoral lesions presents a worse prognosis [73, 74, 76]. Takasaki et al. [61] in Nagasaki, Japan, evaluating 25 smoldering cases without subtyping and 65 chronic ATL patients, observed that the survival was longer for the chronic (5.3 years) in relation to the smoldering form (2.9 years) and even the 5-year survival was longer for the chronic form (50.2% versus 39.4%). Moreover, in this evaluation the progression rate of smoldering ATL was 60%. Another study in Kyushu, Japan, indicated that among 26 smoldering patients 42% progressed to acute ATL. In Bahia, Brazil, only 18% of the smoldering patients progressed to other ATL types [47]. The poor prognosis of the smoldering ATL with cutaneous involvement in Japan is probably due to the inclusion of the PCT type within the smoldering primary cutaneous type [57–62].

In Brazil, among 80 cases of ATL with cutaneous involvement, a statistically significant difference was observed between the median survival time of patients with primary cutaneous ATL (58 months) and those with secondary ATL (10 months) (Fig. 42.16). Furthermore, a longer median survival time was found among cases of primary cutaneous smoldering ATL (109 months) compared with the PCT type (20 months), highlighting the importance of making a clear distinction between these two types of primary cutaneous ATL (unpublished data).

The prognosis of the aggressive forms of ATL is considered poor in view of multidrug resistance of malignant cells, a large tumor burden with multiorgan failure, hypercalcemia, and/or frequent infectious complications as a result of a profound T-cell immunodeficiency [56].

Treatment

The treatment decisions should be based on the ATL classification, prognostic factors at diagnosis, and response to initial therapy [56]. The prognostic factors, among others, include age, performance status [82], clinical and histologic types, primary cutaneous versus secondary ATL, levels of LDH, number of involved lesions, hypercalcemia, thrombocytopenia, eosinophilia, bone marrow involvement, and level of Ki-67 expression [47, 56].

In less aggressive forms it is recommended to manage the patients with supportive care and a watchful waiting approach and/or antivirals, the most frequently used being zidovudine (azidothymidine; AZT) and IFN-α and/or skin-direct treatments (topical steroids, ultraviolet B (UVB) phototherapy, psoralen-UVA photochemotherapy, and radiation therapy). In aggressive ATL the patients are generally treated with chemotherapy, antivirals, and/or bone marrow transplantation (Table 42.7). Although some combinations of chemotherapy produce regression in ATL cases, they failed to achieve a significant impact on long-term survival. Other treatment protocols are being tested, such as anti-CCR4 monoclonal

Table 42.7 Strategy for the treatment of adult T-cell leukemia/lymphoma [56]

Smoldering or favorable chronic type

1. Symptomatic patients (skin lesions, opportunistic infections, and so forth): consider AZT/IFN or watch and wait

2. Asymptomatic patients: consider watch and wait

Unfavorable chronic or acute type

If outside clinical trials, check prognostic factors:

1. Good prognostic factors: consider chemotherapy (VCAP-AMP-VECP evaluated by a randomized phase III trial against biweekly CHOP) or AZT/IFN

2. Poor prognostic factors: consider chemotherapy followed by conventional or reduced-intensity allogeneic HSCT

3. Poor response to initial therapy with chemotherapy or AZT/IFN: consider conventional or reduced-intensity allogeneic HSCT

Lymphoma type

If outside clinical trials, consider chemotherapy (VCAP-AMP-VECP)

Check prognostic factors and response to chemotherapy:

   Favorable prognostic profiles and good response to initial therapy: consider chemotherapy

   Unfavorable prognostic profiles or poor response to initial therapy with chemotherapy: consider conventional or reduced-intensity allogeneic HSCT

ATL adult T-cell leukemia/lymphoma, *AZT* zidovudine, *IFN-α* interferon-α, *VCAP-AMP-VECP* vincristine, cyclophosphamide, doxorubicin, and prednisone; doxorubicin, ranimustine, and prednisone; and vindesine, etoposide, carboplatin, and prednisone, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone, *HSCT* hematopoietic stem cell transplantation. Simplified from Table 1 of Tsukasaki et al. [56], originally published by the American Society of Clinical Oncology

antibody [56, 59, 67, 83–85]. Details of treatment options for all types of ATL and response criteria can be found in these references.

Here we emphasize the treatment of primary cutaneous ATL, but it is necessary to take into account that all papers about the treatment of primary cutaneous ATL or cutaneous ATL do not subtype it, and often include the smoldering in general and the favorable chronic forms under the designation of indolent ATL.

The International Consensus Meeting for Definition, Prognostic Factors, Treatment, and Response Criteria of ATL recommended for smoldering ATL the strategy of watchful waiting until disease progression or AZT/IFN-α [56]. In a world meta-analysis study carried out on the use of antiviral therapy versus chemotherapy, analyzing together 23 smoldering and chronic patients, it was observed that those who received first-line antiviral therapy had a better survival (5-year overall survival of 100%) than patients who received first-line chemotherapy (5-year overall survival of 42%) with or without maintenance antiviral therapy [83]. In addition, it has been shown that chemotherapy may result in a poor outcome for indolent ATL [61]. The problem with the treatment using AZT/IFN-α is that continuous therapy is mandatory even after the disappearance of symptoms, because relapse always occurs when treatment is stopped [85].

Katsuya et al. [59], in a retrospective study including 157 smoldering patients, 76% with skin lesions, considered that the standard care for smoldering ATL is watchful waiting with skin-directed therapy (narrow-band UVB therapy or psoralen photochemotherapy), if needed. Kudo et al. [86] obtained good results with UVB phototherapy in a smoldering primary cutaneous ATL patient with localized plaque. The type of phototherapy has to be chosen according to the degree of infiltration of the skin lesions, UVB being used for the less infiltrated lesions.

Employing skin-direct therapies (UVB or radiation therapy) combined or not with etoposide (daily with 25–75 mg combined with 10–20 mg prednisolone, modifying the periods in individual cases) in 62 patients with smoldering ATL, Sawada et al. [84] obtained a better improvement of the overall survival and progression-free survival with the association of etoposide with skin-directed therapy. We emphasize that combination therapy was employed only in patients with nonlocalized lesions and with more than three nodular tumoral lesions in patients with probable poor prognosis. Complete remission was obtained with combined therapies in 68.4% of patients including two with nodules/tumors, with skin-direct therapy alone in 41.4% of patients, all with patch and plaque, and with solely etoposide in only one (7.1%), a patient with plaque. In a recent evaluation of treatment, in Bahia, Brazil, of 29 primary cutaneous smoldering patients with a median survival time of 109 months, good results were obtained with a median survival time of 169 months in the 19 patients submitted to watchful-waiting management, and 11 of them also to phototherapy (unpublished data). Although the

watchful-waiting approach for the primary cutaneous smoldering form is the most recommended in the literature [56], combination with phototherapy seems to be the best approach as it leads to a complete or partial remission of the cutaneous lesions (unpublished data). It is important to emphasize the need for regular monitoring of these patients, since they may progress to more aggressive forms. When transformation to acute disease occurs patients, may have the treatments indicated to this form [84].

As the PCT form is generally included in the smoldering type, there is no recommendation in the literature about treatment. Notwithstanding, there are rare cases of PCT type reported with data about therapy and follow-up, one of which was diagnosed as PCT and three others as smoldering ATL and cutaneous-type ATL, respectively [87–90]. All of them had confirmed proviral integration and large cells in histopathology. Three presented complete remission, one with administration of AZT/IFN remaining without lesions during 6 months of follow-up [87], another with intralesional corticosteroids [88], and the third, a rare ATL presentation with only one tumor, with radiotherapy. This last patient had no recurrence during 13 months of follow-up [89]. A fourth patient underwent chemotherapy and bone marrow heterologous transplantation, but failed to achieve a sustained remission [90]. In one report, including five PCT cases, radiotherapy to reduce the size of the tumors combined with chemotherapy and/or IFN-α/AZT were used, without good results, the median survival time of being only 20 months [47].

Xerosis and Acquired Ichthyosis

Xerosis is dryness of the skin, while acquired ichthyosis is clinically characterized by cutaneous xerosis with the formation of polygonal thin flat squames of varied sizes, principally on the extremities (Fig. 42.17) [91]. Xerosis and acquired ichthyosis have been described in up to 66.7% of cases of HAM/TSP, being more severe in the more advanced cases of the disease [92]. According to Yamaguchi [93], acquired ichthyosis is a consequence of the hypohidrosis found in these patients, which may result from a lesion of the autonomic nerves. However, carriers of this virus may also have acquired ichthyosis [94]. Among 42 cases of infantojuvenile IDH, xerosis was found in 64% and acquired ichthyosis in 10% of the cases [12].

Another theory regarding the cause of acquired ichthyosis is that it may occur following an inflammatory lesion of the eccrine sudoriferous glands. Nested PCR was used to demonstrate the presence of HTLV-1 infection in the epithelial cells of eccrine sudoriferous glands associated with the presence of lymphocyte infiltrate around these glands. It has been suggested that this inflammatory process may lead to sweat disorders, which would be responsible for drying the skin [95].
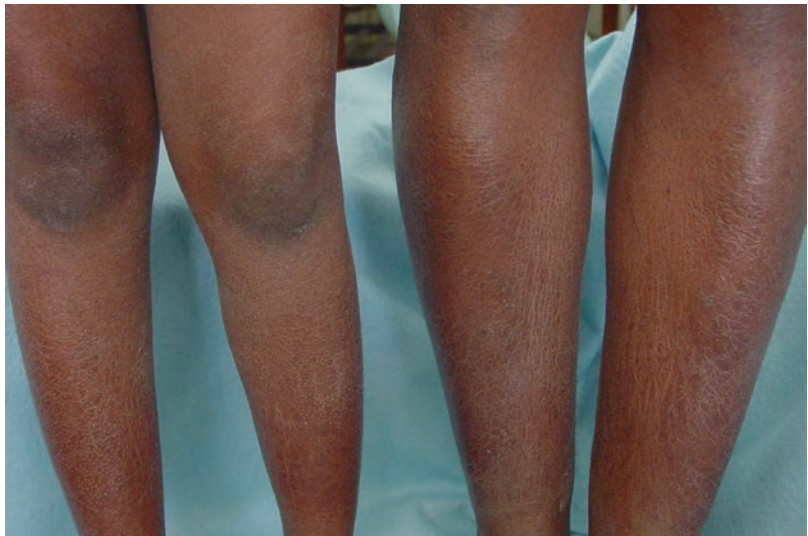
Fig. 42.17 Mother, an HTLV-1 carrier, and daughter with infective dermatitis associated with HTLV-1, both with acquired ichthyosis on the legs

Lenzi et al. [80] evaluated skin biopsies of 32 patients with HAM/TSP and xerosis and found lymphocyte infiltrate in the superficial dermis in seven cases and in the deep dermis in another case, frequently associated with lymphocyte epidermotropism. Atypical lymphocytes were seen in one case. The authors considered these cases to be suggestive of skin lymphoma.

Milagres et al. [91] studied the expression and distribution of keratins K1, K10, K6, K16, involucrin, and the Ki-67 proliferative index of the epidermis in biopsies of HAM/TSP patients with ichthyosis. Taking into consideration the lack of acanthosis and the absence of increased cell kinetics of the epidermis, they concluded that the pattern of acquired ichthyosis related to HTLV-1 is not hyperproliferative but retentive.

An ichthyosis-like pattern may be secondary to diffuse lymphomatous infiltration of the skin (Fig. 42.18); however, clinically, it can be differentiated by the thickness of the skin and by the presence of other lesions. Nevertheless, in cases of doubt biopsy should be performed on the lesion.

Noninfectious Inflammatory Dermatoses

Erythematous patches or plaques may appear in HAM/TSP patients or in HTLV-1 carriers without clinical or laboratory indications of ATL. Histologically a lymphocyte infiltrate with epidermotropism in some cases, albeit with no atypical cells, has been observed [80]. Erythematous lesions of the palms of the hands and the face have already been described as a frequent finding in HAM/TSP, corresponding histologically to perivascular lymphocyte infiltrate [92]. Elevated serum levels of proinflammatory cytokines such as TNF-α have already been reported in HTLV-1 carriers and in patients with HAM/TSP, and this may at least partially explain the occurrence and persistence of these inflammatory skin processes [21].

Seborrheic dermatitis has been reported more frequently among HTLV-1 carriers [94]. Maloney et al. [96] compared 28 HTLV-1 sero-

Fig. 42.18 Secondary ichthyosis in a chronic ATL patient associated with lymphomatous infiltration of the skin

positive with 280 seronegative children and observed that seborrheic dermatitis was five times more likely to be present in the infected children compared with the control group. These authors also reported that eczema not referred to as IDH was twice as likely to be found in the infected children compared with the seronegative group.

Infectious and Parasitic Dermatoses

Some infections and parasitic skin diseases such as dermatophytoses and scabies, including crusted scabies, occur more frequently in HTLV-1-infected individuals [94, 97]. In 91 cases of scabies, Brites et al. [97] detected HIV infection in 50%, HTLV-1 infection in 32%, and both infections in 20%. In a cohort of 42 children with IDH,

64% were found to have scabies and two patients had crusted scabies [12]. Less frequently scabies may appear as disseminated nodules (Fig. 42.19) or with diffuse hyperkeratosis and crusts, named crusted or Norwegian scabies (Fig. 42.20) [17].

Protracted *Treponema pallidum* infection has been known to cause syphilitic chancres in HTLV-1-infected rabbits [98]. Figure 42.21 shows a severe form of secondary syphilis, referred to as malignant syphilis, in an HIV-negative HTLV-1 carrier. This may have been the

result of a comorbid infection with HTLV-1.The lesions healed completely following antisyphilitic treatment [99].

Salvador et al. [100] found a higher prevalence of HTLV-1 (2.5%) in a cohort of leprosy outpatients in comparison with the prevalence in the general population (1.8%). These authors observed that coinfection with HTLV-1 is associated with a high rate of unfavorable leprosy outcomes such as type 1 and 2 reactions and neuritis.

Fig. 42.19 HAM/TSP patient with disseminated nodular scabies. Note numerous papules and nodules
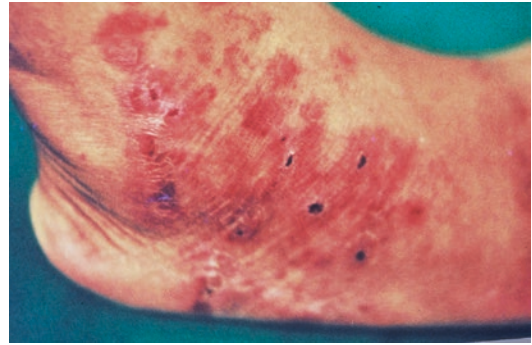
Fig. 42.21 HTLV-1 carrier, HIV negative, with atypical and severe secondary syphilis. Confluent and erythematous papules and plaques on the dorsum of the right foot, some of them with shallow ulcers (Reprinted from Bittencourt and de Oliveira [17])

Fig. 42.20 Norwegian scabies in an acute ATL case without skin lymphomatous lesions

Glossary

Acanthosis Epidermal hyperplasia (thickening of the epidermis). It implies increased thickness of the (stratum spinosum).

Anaplastic nuclei Refers to a group of changes in a cell, loss of polarity (cells may not develop connections to one another), pleomorphism (cells vary in size and shape; their nuclei may also vary in size and shape), hyperchromatism (the nuclei of malignant cells often stain darker than normal cells), abnormal mitoses (division of malignant cells often is abnormal, a feature recognized by "abnormal mitotic figures") that point to a possible malignant transformation.

Clonal proliferation In HTLV-1 infection, is the process in which expansion of infected T cells occur by mitosis. When the proliferation is clonal, the generated cells are identical and all of them have the HTLV-1 provirus integrated in the same site in the host genome. The population of identical infected cells constitutes a clone. Thus, each infected clone can be distinguished from other infected clones by the integration site of the provirus in the host human genome. This process is stimulated by HTLV-1 products.

Crusted scabies A rare, highly contagious uncommon form of scabies characterized by presence of huge number of *Sarcoptes scabiei* in the horny layer of the epidermis. As a reaction, the horny layer thickens and forms warty crusts. In most cases it is associated with some underlying diseases and usually affects immunocompromised patients.

Erythroderma Generalized exfoliative dermatitis. It is a disease characterized by erythema and scaling of greater than 90% of the body's surface.

Folliculotropism and angiotropism The invasion of follicular units and vessel walls by lymphocytes. In malignant conditions the lymphocytes show variable degrees of nuclear atypia.

Hyperkeratosis Thickening of the horny layer of the skin.

Ichthyosis It may be inherited (genetic) or acquired during life. The inherited forms are rare, generally present from infancy, and are usually lifelong conditions. Acquired ichthyosis can develop at any age due to a number of medical problems.

Pagetoid infiltration Pagetoid is a term used in dermatology to refer to "upward spreading" of abnormal cells in the epidermis (i.e., from bottom to top). It is a possible indication of a precancerous or cancerous condition.

Parakeratosis A mode of keratinization characterized by the retention of nuclei in the stratum corneum. Parakeratosis is associated with the thinning or loss of the granular layer and is usually seen in diseases of increased cell turnover.

Pautrier's microabscess One of the well-defined collections of mycosis cells located within the epidermis in T-cell lymphomas mainly in mycosis fungoides. They are atypical lymphocytes clusters in the epidermis with little associated spongiosis.

Rhinorrhea A condition whereby the nasal cavity is filled with a significant amount of mucus fluid. The condition, commonly known as a runny nose, occurs relatively frequently.

Spongiosis A microscopic term referring to increased intercellular fluid in the epidermis (intercellular edema) that physically pulls keratinocytes away from each other. If severe, spongiosis will cause intraepidermal vesicles (spongiotic vesicles).

Xerostomy Dryness of mucous membranes of the oral cavity and pharynx. It is a consequence of salivary gland dysfunction. Saliva plays an important role in maintaining the correct condition of the oral cavity mucosa.

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Connective Tissue Diseases

43

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Cutaneous Lupus Erythematosus

Key Points
- Lupus erythematosus (LE) is a chronic, inflammatory, autoimmune disease. It can affect only the skin (CLE) or also involves internal organs (SLE)
- Several aspects such as genetics, ambient factors, ultraviolet radiation, drugs, infections, inflammatory cells, cytokines, and chemokines participate in the LE pathogenesis

- There are three major forms of CLE: acute (ACLE), subacute (SCLE), and chronic (CCLE)
- Skin biopsy may include findings such as degeneration of the basal cells, dermal mucin deposits, and thickening of the basement membrane
- Treatment includes topical corticosteroids, antimalarials, sun protection, cessation of smoking.

Introduction

Lupus erythematous (LE) is a chronic, inflammatory, autoimmune disease with a wide clinical spectrum and a variable evolution, severity, and prognosis. LE can manifest only as a dermatologic disease, termed cutaneous LE (CLE). Systemic LE (SLE) commonly involves the skin, joints, and several internal organs.

General Epidemiology

The incidence of LE varies according to the characteristics of the population studied, such as predominant age or sex, race, ethnicity, national origin, or period of time studied, and criteria in diagnostic classification [1–5].

In patients with exclusively cutaneous disease, there is a female-to-male ratio of 3:1. On the other hand, SLE usually affects women during their reproductive years with a female-to-male ratio of 9:1 [6, 7].

Ethnicity is also a major risk factor, the prevalence of SLE being four-fold higher in African American women than in Caucasian American women [6, 7]. African American patients with SLE develop disease at an earlier age and have a higher mortality rate because of organ damage such as nephritis and pneumonitis [6, 7].

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Skin Manifestations

In all types of LE, the skin is one of the most frequent sites of involvement. In 1981, James N. Gilliam divided the cutaneous manifestations of LE into those lesions that show histologic changes characteristic of LE (LE-specific skin disease) and those that are not specific for lupus (LE-nonspecific skin disease). CLE refers to LE-specific skin disease and are divided in three major categories: acute CLE (ACLE), subacute CLE (SCLE), and chronic CLE (CCLE) [8]. Moreover, in addition to the classic forms of CLE, uncommon variants often lead to diagnostic difficulties.

Etiopathogenesis

LE is characterized by a mixture of clinical, histologic, immunopathologic, and laboratory findings. The pathogenetic mechanisms responsible for LE-specific skin disease are not fully understood, although recent work has provided many new insights [9–11].

Genetic

Genetics plays an important role in the development of LE. For example, in monozygotic twins with lupus there is a 25% concordance rate compared with a 2% concordance for dizygotic twins [12]. Numerous lupus-associated genes have been identified, and lupus-associated genetic changes have been linked to the clearance of nuclear debris, apoptotic cells, and immune complexes [13].

Some major histocompatibility complex class I and II alleles may confer susceptibility to CLE, such as human leukocyte antigen (HLA) B8, DR3, DQA1, and DRB1 [9]. Rare mutations also contribute to LE pathogenesis [14].

Ultraviolet

Sun exposure can induce the skin lesions of LE or exacerbate the clinical course in a susceptible person [15]. Moreover, cutaneous findings are most frequently found on sun-exposed skin, and lesions can be induced by exposure to arti-ficial sources of ultraviolet (UV) radiation [3, 16–18]. UV light effects include induction of an inflammatory response and generation of apoptotic keratinocytes or "sunburn cells." UV radiation–induced apoptosis causes presentation of autoantigens that can be involved in LE pathogenesis [9].

Infection

Infectious agents can break immunologic tolerance to self-antigens and induce autoimmune disorders [19]. In LE patients, Epstein–Barr virus (EBV), cytomegalovirus, parvovirus B19, and retrovirus (HRES-1, ERV-3, HERV-E 4-1, HERV-K10, and HERV-K18) infections may have an important pathogenetic role [20, 21]. Infections can participate as primers, inducing responses against self-antigens and promoting activation or apoptosis of several immune cells in genetically predisposed individuals [19].

Hormones

LE is a disease with female predilection, suggesting a hormonal influence. High levels of estrogen and progesterone promote humoral autoreactivity, reinforcing the hormonal theory [22]. Oral contraceptives have been thought to produce disease flares [23, 24].

Drugs and Chemicals

Certain medications can induce both CLE and SLE, such as procainamide, isoniazid, quinidine, chlorpromazine, terbinafine, calcium channel blockers, hydrochlorothiazide, and anti–tumor necrosis factor-α (TNF-α) medications, with more than 90 drugs described [25–27]. Clinical and serologic manifestations normally resolve after withdrawal of the suspected medication [25].

Tobacco has been suggested to predispose to the onset or worsening of lupus [28]. Patients who smoke tend to be less responsive to antimalarial treatment in discoid LE.

Apoptosis

Apoptosis is programmed cell death which can be triggered by internal factors, such as DNA mutation, or by external factors, such as infec-

tions and UV exposure [10]. Some lupus patients demonstrate increased spontaneous apoptosis or impaired clearance of apoptotic peripheral blood cells [29]. Abnormalities in the clearance of apoptotic cells can generate autoantigens and autoimmune diseases.

Innate Immune System

Dendritic cells (DCs) are important in LE pathogenesis by phagocytosis, B-cell activation, and secretion of cytokine-like interferon (INF)-α, interleukin (IL)-6, and B-lymphocyte stimulator (BLyS) [13]. Patients with LE have impaired phagocytosis of apoptotic cells by the DCs. They also can recognize damage-associated molecular pattern, from microbial and endogenous ligands by pathogen recognition receptors (PRR), mainly Toll-like receptors (TLR). TRL 7, TLR 9, TRL 3, and TRL 8 are important because they can recognize nucleic acids [10]. In addition, several lupus genes encode proteins that mediate or regulate TLR signals and are associated with increased plasma IFN-α [14]. Studies have shown a good correlation between expression of IFN-α-inducible genes and SLE activity, suggesting that the increased IFN activity might contribute to increased immune system activity and tissue damage [10].

Very recently, the role of neutrophils has gained special attention in the lupus pathogenesis [14]. These cells can release chromatin structures called neutrophil extracellular traps (NETs). NETs can trap and kill various bacterial, fungal, and protozoal pathogens, and their release is one of the first lines of defense against pathogens, in a process called NETosis. NETs are able to stimulate DCs to produce IFN-α through, for example, interaction with TLR9 [11]. NETosis has been involved in autoimmune pathogenesis, including LE.

Adaptive Immune System

The combined T- and B-cell abnormalities in SLE result in the production of pathogenic autoantibodies.

B lymphocytes act as antigen-presenting cells and also produce antibodies and cytokines in autoimmune diseases. B-cell tolerance is changed in LE, resulting in autoreactive B cells that induce the production of pathogenic autoantibodies [13]. Several of these autoantibodies are thought to be directly pathogenic, including double-stranded DNA (dsDNA) and Ro/SS-A antibodies, hallmarks of SLE patients. Moreover, B lymphocytes present efficiently autoantigens and activate T cells, amplifying the inflammatory cascade [10].

CD4 T cells are critical players in the pathogenesis of lupus since they regulate B-cell responses and tolerance regulation, and also infiltrate target tissues, leading to tissue damage [10]. In early phase of CLE skin lesions, there is a predominance of CD4 T cells, whereas in the late phase CD8 T cells are more abundant [30]. A T-helper 1 (Th1)-mediated immune response is described in CLE [9, 30].

Th17 cells are responsible for induction of inflammation and autoimmunity through release of IL-17, IL-22, and IL-21. Studies have found these cells in CLE and SLE target tissues [10, 11].

Natural regulatory T cells (Tregs) are important in the prevention of abnormal autoimmune responses. They regulate activities of DCs, monocytes, mast cells, B cells, and CD4 and CD8 T cells. Tregs secrete cytokines as IL-10 and transforming growth factor β (TGF-β), which have inhibitory effects in T cells [9]. In CLE Treg cells are reduced in the lesions but not in the circulation as seen in SLE, suggesting an organ-specific Treg cell defect [9].

Cytokines and Chemokines

Cytokines such as IL-6, IL-10, IL-12, IL-17, and IL-18 have been implicated in the immunopathogenesis of CLE [13]. TNF-α may promote autoreactivity in lupus [30].

Clinical Presentation

In 2012 the revised classification for SLE was proposed. According to the Lupus International Collaborating Clinics (SLICC), patients must meet at least four criteria, including at least one clinical

and one immunologic criterion. Alternatively, patients must have biopsy-proven lupus nephritis in the presence of antinuclear and anti-dsDNA.

Cutaneous lesions of LE may be divided into three major forms: acute cutaneous lupus erythematous (ACLE), subacute lupus erythematous (SCLE), and chronic cutaneous lupus erythematous (CCLE). Recently a fourth form has been added to lupus classification, intermittent cutaneous lupus erythematous [31, 32].

Chronic Cutaneous Lupus Erythematous

CCLE can be subclassified into discoid, profundus, and tumidus.

The most common form of cutaneous lesions is the *discoid* form characterized by scaly plaques with dyschromia (usually hyperpigmentation associated with depigmentation) and atrophy (Fig. 43.1). This form of lupus is rarely associated with systemic disease, which occurs in 5–10% of cases. Histologically there is a lymphocytic infiltrate in the dermis–epidermis junction with dermal atrophy. Keratinocyte damage and hyperkeratosis are very characteristic. The dermal–epidermal basement membrane zone is thickened. Hair follicles are involved with damage of keratinocytes and follicular plugging. Dermal mucin deposits may be present.

Lupus profundus is a rare form of CCLE and is characterized by deep nodules involving subcutaneous tissues of proximal extremities, buttocks, face, and trunk, which progress to

Fig. 43.1 Discoid lupus erythematous. Scarred, dyschromic lesions on the face

Fig. 43.2 Lupus profundus. Deep nodules on the face. Lipoatrophy and scars

Fig. 43.3 Lupus tumidus. Erythematous plaque on the face

lipoatrophy and scars (Fig. 43.2). Histologically there is a lobular lymphocytic panniculitis.

Lupus tumidus is also a rare manifestation of CCLE and is characterized by erythematous urticarial papules and plaques with annular or centrifugal presentation on the face, proximal upper extremities, and chest (Fig. 43.3). Histologically there is a perivascular and periadnexal lymphocytic infiltrate associated with mucin deposits.

Some authors classify lupus erythematous tumidus as a separate group as intermittent subtype of CLE [32].

SCLE is characterized by annular and papulosquamous lesions with marked photosensitivity (Fig. 43.4). Many times lesions may resemble psoriasis and are often arranged in a reticulated pattern. Usually, arms and torso are involved and the

Fig. 43.4 Subacute lupus. Annular lesions on the arms

Fig. 43.5 Acute cutaneous lupus erythematosus. Butterfly rash on the center of the face

face is spared. Histologically a common finding is keratinocyte damage and epidermal atrophy. Hydropic degeneration of basal cell layers may be present. Some necrotic keratinocytes may be found in the epidermal layer. The lymphohistiocytic infiltrate is concentrated in the upper dermis with interface and perivascular pattern. The infiltrate tends to be less dense than in discoid cases.

In contrast to CCLE, where there is rarely systemic involvement, half of the patients with SCLE will develop signs and symptoms of SLE.

ACLE is the form most involved with systemic symptoms and is characterized by butterfly rash in the center of the face or a generalized maculopapular exanthema (Fig. 43.5). Histologically the findings are nonspecific and similar to those of dermatitis without significant hyperkeratosis or epidermal atrophy.

The principal characteristics of the three major forms of lupus are summarized in Table 43.1.

Some skin lesions are not specific of LE and are often seen in patients with SLE and other autoimmune diseases. Those include cutaneous vascular disease such as vasculitis and vasculopa-

thies, periungual telangiectasias, livedo reticularis, Raynaud's phenomenon, nonscarring alopecia, rheumatoid nodules, calcinosis cutis, urticaria, leg ulcers, lichen planus, and chilblains [33]. Some specific and nonspecific skin findings in cutaneous lupus erythematous are summarized in Table 43.2.

Cutaneous Lupus Erythematous Variants

Neonatal lupus erythematosus is a rare condition in the neonatal period whereby children have lesions similar to those of SCLE and/or congenital heart block. There is an associated with maternal immunoglobulin G (IgG) antinuclear antibodies. Congenital heart block may require a pacemaker. The children may also have photosensitivity, hepatobiliary disease, hemolytic anemia, thrombocytopenia, and leukopenia [33].

In *bullous lupus erythematosus*, patients have blisters that resemble dermatitis herpetiformis or bullous pemphigoid. Blisters may appear as a result of the intense of the basal cell damage. A second situation is when the blisters are formed by an intense neutrophilic infiltrate in the dermal papillae resembling dermatitis herpetiformis [34].

Hypertrophic lupus is characterized by solitary verrucous and hyperkeratotic lesion [33].

Rowell's syndrome is characterized by skin lesions similar to erythema multiforme and occurs in patients with an established history of LE.

Drug-induced lupus erythematosus is more associated with some drug classes, although

Table 43.1 Principal characteristics of the three major forms of cutaneous lupus erythematous

	Acute	Subacute	Chronic
Clinical	Butterfly rash *OR* generalized maculopapular exanthema	Psoriasiform	Scaly dyschromic plaques
		Annular lesions	Atrophy
		Marked photosensitivity	
Probability of systemic involvement	High	Intermediate	Low
Antibody profile	ANA positive (high titers)	anti-Ro/SS-A and anti-La/SS-B	None *OR* ANA positive (low titers)
Histology	Nonspecific, resembling dermatitis	Similar to discoid with less intense infiltrate	*Discoid*: lymphocytic infiltrate in the dermis–epidermis junction with dermal atrophy. Keratinocyte damage and hyperkeratosis. Follicular involvement
			Panniculitis: lobular lymphocytic panniculitis
			Tumidus: dermal perivascular and periadnexal lymphocytic infiltrate and mucin deposits. Sparse epidermal findings

ANA antinuclear antibody

Table 43.2 Specific and nonspecific skin findings in cutaneous lupus erythematous

Specific lesions	Nonspecific lesions
Acute cutaneous lupus erythematous (ACLE)	Raynaud's phenomenon
Subacute lupus erythematous (SCLE)	Thrombophlebitis
Chronic cutaneous lupus erythematous (CCLE)	Nailfold telangiectasias
	Diffuse nonscarring alopecia
	Calcinosis
	Vasculitis
	Livedo reticularis

more than 40 drugs have been involved. Terbinafine and TNF-α inhibitors are drugs with a high risk of development. Antihypertensives, antipsychotics, anticonvulsants, antihistamines, anti-inflammatories, antimicrobials, and immunosuppressives are all drug classes associated with this form of LE. Patients develop positive antinuclear antibodies (ANA) [35].

Many conditions have to be considered in the differential diagnosis of CLE (Table 43.3).

Complementary Examinations

A skin biopsy may demonstrate some characteristics that corroborate the diagnosis. Each clinical presentation has some specific characteristics in pathology, as discussed previously, and also are related to the stages of the lesions [36]. Degeneration of the basal cells of the epidermis (hydropic degeneration) associated with lympho-histiocytic cellular infiltrate is typical of LE. The hair follicle structure may be involved with keratotic plug. Dermal mucin deposits favor the diagnosis of lupus [34, 35] (Table 43.4).

Direct immunofluorescence of lesional skin may demonstrate granular deposits at the dermal–epidermal junction and around hair follicles. Typically, these are formed by IgG and/or IgM deposits. Complement proteins are also common. Presence of antibody deposits at the dermal–epidermal junction from a normal-appearing skin is called "lupus band" and correlates with systemic disease. Nevertheless, the absence of deposits does not rule out lupus diagnosis [34].

To rule out SLE, ANA profile, urinalysis, complete blood count with differential, platelets count, chemistries, erythrocyte sedimentation rate, and complement levels should be required. Clinically patients with history of diffuse nonscarring alopecia, periungual telangiectasia, Raynaud's phenomenon, livedo reticularis, vasculitis, and lymphadenopathy should be investigated for SLE [34].

Table 43.3 Differential diagnosis of cutaneous lupus erythematosus

Chronic cutaneous lupus erythematosus (CCLE)	Subacute cutaneous lupus erythematosus (SCLE)	Acute cutaneous lupus erythematosus (ACLE)
Actinic keratosis	Plaque psoriasis	Dermatomyositis
Granuloma faciale	Lichen planus	Drug eruptions
Granuloma annulare	Erythema annulare centrifugum	Drug-induced photosensitivity
Keratoacanthoma	Tinea corporis	Seborrheic dermatitis
Lichen planus	Mycosis fungoides	Acne rosacea
Plaque psoriasis	Nummular eczema	
Cutaneous squamous cell carcinoma	Pityriasis rubra pilaris	
Panniculitis	Polymorphous light eruption	
	Sarcoidosis	

Table 43.4 Histologic findings in CLE

Hyperkeratosis with follicular plugging
Epidermal atrophy
Dermal atrophy
Hydropic degeneration of the basal layer
Lymphohistiocytic cellular infiltrate
Apoptotic keratinocytes (Civatte bodies)
Thickening of the basement membrane
Interstitial mucin deposition
Atrophy of pilosebaceous units

Positivity for ANA varies accordingly to the form of lupus. CCLE is rarely associated with systemic disease but low titers of ANA may be present. ACLE is highly associated with systemic involvement and ANA is usually present in high titers. SCLE has an intermediate association with SLE (50% fulfillment criteria for SLE) and usually is associated with positivity for anti-Ro/SSA antibody (70% of cases), ANA (60–70%), and anti-La/SSB (30–50%) [33].

Therapeutic Approach

Treatment includes topical steroids and calcineurin inhibitors such as tacrolimus 0.1% ointment. The latter may be a good alternative because of its fewer side effects, rapid onset, and safety during long-term use [37].

Antimalarials modulate the immune response without increasing the risk of infections. Hydroxychloroquine is associated with skin pigmentation and ocular toxicity. The response with these drugs may be slow and take 2–3 months.

Dapsone and retinoids are used as second-line therapy, especially in patients without response to antimalarials. Thalidomide is also an alternative but is associated with a high risk of relapse and neurotoxicity. Thalidomide analogs such as lenalidomide have less neurotoxicity and may be a good alternative [37]. Other options include immunosuppressors such as mycophenolate mofetil, azathioprine, systemic steroids, sulfasalazine, and cyclophosphamide. For bullous eruption of SLE dapsone may be useful. More recent studies suggest immunobiological drugs such as belimumab as a possible therapeutic alternative [37].

It is believed that UV radiation may induce systemic manifestations and specific skin lesions in LE disease [38]. Skin protection using broad-spectrum sunscreens is recommended in combination with physical protection with clothes and accessories. Although there is an evident association between photosensitivity and LE, light therapies may be an option for recalcitrant cutaneous manifestations [39].

Interestingly, there may be an association between vitamin D deficiency and lupus. Vitamin D has many functions in cellular growth and immune function. In CLE patients, low levels of vitamin D are associated with higher IFN levels and disease activity. Patients with SLE after vitamin D supplementation had lower disease activity scores and decreased anti-DNA antibody level [40]. The levels of vitamin D and calcium should be monitored in these patients.

The definitive role of smoking in lupus is not well established. Current smokers have an increased risk for SLE/CLE, higher disease activ-

Table 43.5 First- and second-line approaches for CLE treatment

First-line therapy	Second-line therapy
Sun protection	Dapsone
Quit smoking	Retinoids
Topical steroids	Thalidomide
Antimalarials	Immunosuppressors

ity scores, and higher frequency of anti-dsDNA compared with ex-smokers or those who never smoked [37]. Smoking is associated with cutaneous manifestations in SLE. Some authors suggest that CLE, but not SLE, is associated with smoking [41]. Smoking is associated with a two-fold decrease in the proportion of patients with CLE achieving cutaneous improvement with antimalarials [42].

First- and second-line approaches for CLE are summarized in Table 43.5.

Dermatomyositis

Key Points
- Dermatomyositis is an autoimmune disease that classically affects skin and muscles
- Vigilance for important associations with lung disease and malignancy can be aided by serology testing
- Distinctive skin findings are readily identifiable and assist in diagnosis
- Dermatomyositis therapy involves the use of corticosteroids, typically with an immunosuppressive agent

Introduction

Dermatomyositis is an idiopathic inflammatory myopathy with characteristic cutaneous findings that occur in children and adults. This systemic disorder most frequently affects the skin and muscles but may also affect the joints, the esophagus, the lungs, and, less commonly, the heart [43, 44]. Dystrophic calcinosis may complicate dermatomyositis and is most often observed in children and adolescents. An association between

dermatomyositis and cancer has long been recognized in adult patients.

General Epidemiology

The estimated incidence of dermatomyositis is 9.63 cases per million population. The estimated incidence of amyopathic dermatomyositis is 2.08 cases per million [45].

Dermatomyositis can occur in people of any age. Two peak ages of onset exist: in adults, the peak age of onset is approximately 50 years, whereas in children it is approximately 5–10 years. Dermatomyositis and polymyositis are twice as common in women as in men. Neither condition shows any racial predilection.

Etiopathogenesis

The cause of dermatomyositis is unknown. However, genetic, immunologic, infectious, and environmental factors have been implicated.

A *genetic* component may predispose to dermatomyositis. Dermatomyositis rarely occurs in multiple family members, but a link to certain HLA types (e.g., DR3, DR5, DR7) may exist.

Polymorphisms of TNF may be involved; specifically, the presence of the -308A allele is linked to photosensitivity in adults and calcinosis in children [46, 47, 48]. A meta-analysis demonstrated that the TNF-α-308A/G polymorphism might contribute to dermatomyositis susceptibility, especially in a European population [49].

Immunologic abnormalities are common in patients with dermatomyositis. Patients frequently have circulating autoantibodies. Abnormal T-cell activity may be involved in the pathogenesis of both the skin disease and the muscle disease. In addition, family members may manifest other diseases associated with autoimmunity.

ANAs and antibodies to cytoplasmic antigens (i.e., antitransfer RNA synthetases) may be present. Although their presence may help to define subtypes of dermatomyositis and polymyositis, their role in pathogenesis is uncertain.

Infectious agents have been suggested as possible triggers of dermatomyositis. These include the following: viruses (e.g., coxsackievirus, parvovirus, echovirus, human T-cell lymphotropic virus type 1 (HTLV-1), human immunodeficiency virus (HIV)), *Toxoplasma* species, and *Borrelia* species.

Cases of *drug-induced* dermatomyositis have been reported. Dermatomyositis-like skin changes have been reported with hydroxyurea in patients with chronic myelogenous leukemia or essential thrombocytosis [50, 51].Other agents that may trigger the disease include the following: statins, penicillamine, anti-TNF drugs, IFN, cyclophosphamide, bacillus Calmette-Guérin (BCG) vaccine, quinidine, phenylbutazone.

Dermatomyositis may be initiated or exacerbated by silicone breast implants or collagen injections, but the evidence for this is anecdotal and has not been verified in case–control studies. One report detailed HLA differences among women in whom inflammatory myopathy developed after silicone implants [52].

Clinical Presentation

The distinctive skin findings of dermatomyositis are periorbital erythema and swelling described as a heliotrope rash (Fig. 43.6). Redness and papules overlying the knuckles are called the papules of dermatomyositis (Gottron papules) and are often seen in conjunction with ragged cuticles, dilated nailfold capillaries, and cuticle hemorrhage (Fig. 43.7).

A less common hand finding is hyperkeratosis along the sides of the fingers and on the palms, sometimes with surrounding erythema known as mechanic's hands.

The finding of erythema, hypopigmentation and hyperpigmentation, and telangiectasia extending over the shoulders, in a V distribution of the neck and lateral thighs, is often described as poikiloderma associated with dermatomyositis (Fig. 43.8). Scale is often present, and the rash is difficult to distinguish from lupus or other papulosquamous disorders. Attention to the characteristic distribution and careful examination of the nailfolds is helpful in these cases. Scalp involvement with erythema, scale,

Fig. 43.6 Dermatomyositis. Heliotrope (periorbital erythema and swelling)

Fig. 43.7 Gottron papules. Erythematous papules overlying the knuckles

and often intense pruritus can persist even when other areas of skin involvement have come under control [53].

Conditions to be considered in the differential diagnosis of dermatomyositis are summarized in Table 43.6.

Complementary Examinations

Skin biopsy is not specific, but can support the diagnosis of dermatomyositis. It shows features

Fig. 43.8 Dermatomyositis. Poikiloderma

Table 43.6 Dermatomyositis: differential diagnosis

Lupus erythematosus
Graft-versus-host disease
Lichen myxedematosus
Lichen planus
Multicentric reticulohistiocytosis
Psoriasis
Parapsoriasis
Polymorphous light eruption
Rosacea
Tinea corporis
Sarcoidosis

similar to those of lupus, with interface dermatitis and perivascular lymphocytic inflammation. Along with strength testing, detection of increased muscle enzyme levels in serum can indicate muscle involvement. Levels of creatine kinase, lactate dehydrogenase, aldolase, aspartate aminotransferase, and alanine aminotransferase are all potentially increased in muscle disease, and checking several is reasonable. Although the complete evaluation of muscle disease is not discussed here, it is important to remember that once dermatomyositis has caused extensive

damage to the muscles and atrophy has occurred, the muscle enzyme levels may return to normal despite significant muscle disease.

A positive ANA test occurs in 80–90% of patients. In addition, multiple myositis autoantibodies can be detected, and increasing relevance and clinical implications are being recognized for these antibodies (Table 43.7) [54]. Clinically important antibodies include Mi-2, MDA5, anti-p155/140, and antisynthetase antibodies. Mi-2 is most specific for dermatomyositis but is not very sensitive. When present, it suggests treatment-responsive disease.

The constellation of rapidly progressive severe interstitial lung disease, myositis, arthritis (often mechanic's hands), and antisynthetase antibodies, sometimes with SSA antibodies, is referred to as the antisynthetase syndrome [55, 56]. Fever and Raynaud's phenomenon may be additional symptoms. There have been eight distinct antisynthetase antibodies detected, and more are likely be to be found in the future. Of these, anti-Jo-1 is the most common. In some cases, lung disease is the initial presenting symptom and other features are less prominent [57].

The presence of MDA5 antibodies is also associated with severe interstitial lung disease [58]. It is found in amyopathic forms of dermatomyositis and may be associated with punched-out-type ulcerations in the skin.

Overlaps exist between dermatomyositis and lupus, as well as systemic sclerosis. In these presentations, a variety of autoantibody patterns can be seen, including positive SSA, anti-RNP, anti-sm, and SCL.

An association between dermatomyositis and malignancy is well recognized. The clinical findings of dermatomyositis may precede, coincide with, or follow the cancer diagnosis. Recent analysis has suggested a five-fold greater occurrence of cancer in these patients than would normally be expected [59]. The malignancies most represented in the setting of dermatomyositis are hematopoietic and lung. A variety of other cancers are also noted to be over-represented, including ovary, colon, bladder, breast, cervix, pancreas, and esophagus [59, 60]. Cancer screening recommendations are not standardized. Consequently, appropriate clinical decision mak-

Table 43.7 Frequency of antibodies in dermatomyositis (DM) and clinical associations

Antibody	Frequency in DM (%)	Clinical association
Mi-2	20–30	Most specific antibody for DM. More responsive disease
MDA5	50	Associated with amyopathic DM. Increased ILD and skin ulcers; levels may decrease in response to therapy
P155/140	20–25 40–75, cancer-associated DM	Cancer-associated myositis, severe skin disease, high negative predictive value for malignancy
Antisynthetase (Jo-1 and others)	5–10	Antisynthetase syndrome high frequency of ILD and arthritis

ILD Interstitial lung disease

ing includes symptom-directed screening and the usual age-appropriate screening. It is reasonable to repeat the screening annually for 3 years, because this is when the risk of cancer-associated dermatomyositis tends to decrease. Because routine screening is not very effective for ovarian cancer, lung cancer, and pancreatic cancer, vaginal ultrasonography and a computed tomography scan of the chest, abdomen, and pelvis is ordered by some experts.

Therapeutic Approach

Although treatment algorithms do not exist for dermatomyositis, a common approach is to start oral prednisone at doses around 1 mg/kg/day for patients with evidence of muscle disease. This dose is tapered slowly, often over months. With long courses of steroids, side effects are a predicted complication. Concurrent addition of a steroid-sparing immunosuppressive drug may shorten the need for high-dose steroids and prevent steroid-associated side effects. Commonly used therapies are methotrexate (10–20 mg per week), mycophenolate (1,000–1,500 mg twice daily), or azathioprine. Often these can be started at the same time as prednisone. In cases resistant to standard therapy, intravenous immunoglobulin or rituximab are reasonable choices. For interstitial lung disease, a more aggressive treatment regimen is usually required.

Once therapy has been initiated it seems that exercise, both resistance and aerobic, may benefit patients with myositis. It is reasonable to recommend an exercise program after about 4 weeks of systemic treatment [61].

Skin disease in patients with dermatomyositis can be resistant, and attention to skin-specific treatments is important.

Photoprotection is recommended, with clothing and broad-spectrum sunscreen. Midpotency topical steroids and topical calcineurin inhibitors are also helpful for the rash and related itching.

Addition of hydroxychloroquine or chloroquine can benefit patients significantly.

In patients with amyopathic forms, escalation of therapy to other systemic agents, including methotrexate and mycophenolate, may be required to control symptoms [44].

Morphea

Key Points
- Morphea is an idiopathic inflammatory skin disease that causes skin hardening and in some cases loss of function
- Although understanding of the pathophysiology is incomplete, it seems to share features with systemic sclerosis
- Despite this common pathophysiology, morphea and systemic sclerosis are readily distinguished clinically and should be thought of separately
- Morphea is largely confined to the skin and subcutaneous tissues, whereas systemic sclerosis is a multisystem disease

Introduction

Morphea, also known as localized scleroderma, is a disorder characterized by excessive collagen deposition leading to thickening of the dermis, subcutaneous tissues, or both. Morphea is classified into circumscribed, generalized, linear, and pansclerotic subtypes according to the clinical presentation and depth of tissue involvement [62]. Unlike systemic sclerosis, morphea lacks features such as sclerodactyly, Raynaud's phenomenon, nailfold capillary changes, telangiectasias, and progressive internal organ involvement. Morphea can present with extracutaneous manifestations, including fever, lymphadenopathy, arthralgias, fatigue, and central nervous system involvement, as well as laboratory abnormalities, including eosinophilia, polyclonal hypergammaglobulinemia, and positive ANA [62–65].

Although rare, epidemiologic studies suggest that 0.9–5.7% of patients with morphea progress to systemic sclerosis [64]. The transition may be marked by the development of Raynaud's phenomenon and nailfold capillary changes. However, these patients may have been initially misclassified on diagnosis.

General Epidemiology

The incidence of morphea has been estimated as approximately 0.4–2.7 per 100,000 people [66]. The actual incidence is likely higher because many cases may not come to medical attention. Two-thirds of adults with morphea present with plaque superficial circumscribed lesions, with generalized, linear, and deep variants each accounting for approximately 10% of cases. Up to half of all cases of morphea occur in pediatric patients. In this group, linear morphea predominates (two-thirds of cases), followed by the plaque superficial circumscribed (25%) and generalized (5%) subtypes. Of note, as many as half the patients with linear morphea have coexistent plaque-type lesions.

Although morphea occurs in persons of all races, it appears to be more common in whites, who represent 73–82% of patients seen [66].

Women are affected approximately three times as often as men for all forms of morphea except the linear subtype, which only has a slight female predominance.

Linear morphea commonly manifests in children and adolescents, with two-thirds of cases occurring before age 18 years. Other morphea subtypes have a peak incidence in the third and fourth decades of life.

Etiopathogenesis

The cause of morphea is unknown. An autoimmune mechanism is suggested by an increased frequency of autoantibody formation and a higher prevalence of personal and familial autoimmune disease in affected patients [65, 67]. Patients with generalized morphea are more likely to have a concomitant autoimmune disease, positive serology for autoantibodies, particularly ANA, and systemic symptoms [65]. To date, investigations have not described any consistent etiologic factors. Different morphea subtypes often coexist in the same patient, suggesting that the underlying processes are similar. The following are causes and associations.

Radiation therapy Morphea can occur at the site of previous radiation therapy for breast cancer and other malignancies, developing from 1 month up to more than 20 years after irradiation [68, 69]. Involvement may extend beyond or distant to the irradiation field [66].

Infections, such as EBV infection, varicella, measles, hepatitis B, and borreliosis, have been reported to precede the onset of morphea and have been proposed as possible triggers [70].

Chimerism Immature chimeric cells have been found in morphea lesions, suggesting that such nonself cells may lead to an autoimmune phenotype [71].

Vaccinations Morphea-like lesions have also been reported to occur following vaccinations, including BCG, tetanus, and mumps-measles-rubella vaccinations. Whether the vaccinations

themselves or the trauma from the injections was the inciting event is not clear.

Drug-induced morphea This is only rarely reported (i.e., from bisoprolol, bleomycin, D-penicillamine, L-5-hydroxytryptophan, balicatib) [66, 72].

Trauma Some morphea patients report a history of local trauma directly preceding the onset of disease. Plaques of circumscribed morphea often develop in areas of pressure. Reports of morphea lesions following vitamin B-12 and vitamin K injections suggests that trauma from injections may play a role [66].

Overproduction of collagen, particularly types I and III collagen, by fibroblasts in affected tissues is common to all forms of morphea, although the mechanism by which these fibroblasts are activated is unknown. Proposed factors involved in the pathogenesis of morphea include endothelial cell injury, immunologic (e.g., T-lymphocyte) and inflammatory activation, and dysregulation of collagen production. An autoimmune component is supported by the frequent presence of autoantibodies in affected individuals, as well as the association of morphea with other autoimmune diseases, including SLE, vitiligo, type 1 diabetes, and autoimmune thyroiditis [63, 65].

Endothelial cell injury is currently thought to be the inciting event in the pathogenesis of morphea. This injury results in increased levels of adhesion molecules (circulating intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and E-selectin) and fibrogenic Th2 cytokines such as IL-4, IL-6, and TGF-β. These cytokines recruit eosinophils, CD4$^+$ T cells, and macrophages, which are present in early morphea lesions and in eosinophilic fasciitis. These cytokines and growth factors also increase fibroblast proliferation and induce synthesis of excess collagen and connective-tissue growth factor. TGF-β also decreases production of proteases, inhibiting collagen breakdown [66].

Connective-tissue growth factor is a soluble mediator that enhances and perpetuates the profibrotic effects of TGF-β. The ultimate result of the endothelial injury and inflammatory cascade is increased collagen and extracellular matrix deposition [73–76]. Other proposed pathophysiologic mechanisms in morphea include the formation of anti-matrix metalloproteinase antibodies, as well as increased expression of insulin-like growth factor, which enhances collagen production [77, 78].

Clinical Presentation

The onset of symptoms in morphea may be insidious, and studies have shown a delay in diagnosis of a year or longer [79]. Patients may describe arthralgias, myalgias, and fatigue occurring along with morphea but the systemic symptoms of gastrointestinal reflux, pulmonary symptoms, and cardiac symptoms seen in systemic sclerosis are not characteristic of morphea [80].

In addition to the skin findings, there are some special clinical considerations in patients with morphea. Morphea that involves the scalp or occurs around the eyes can be associated with symptoms of uveitis, headaches, or seizures [81, 82]. Several reports show a strong association between morphea and genital lichen sclerosis. Frank discussion with patients about genital symptoms, including skin changes, itching, or burning, should be included in the history because patients may be reluctant to volunteer these concerns [83].

The course of morphea is one of remission and relapse [84]. Ongoing monitoring is helpful to treat relapses early and avoid additional disability.

Plaque morphea Several distinct patterns of morphea occur on the skin. Plaque-type morphea is the most common. The earliest lesions are often erythematous plaques with little induration; sometimes a lilac border is observed at the periphery of the lesion (Fig. 43.9). This condition progresses to central sclerosis with induration and smooth yellow to white scarring. There is often peripheral erythema or hyperpigmentation. Over time, destruction of the hair and sweat glands occurs in the affected skin. The plaques can increase in size and number. Involvement in the inframammary

Fig. 43.9 Plaque morphea. Erythematous plaques with induration on mammary area

area, the area around the hips, and on the lower back together as a pattern is common.

Generalized plaque morphea When the plaques are greater than 3 cm in size and there are more than four plaques involving two body areas, it is classified as generalized plaque morphea. Patients can have superficial or deep involvement in the skin.

Pansclerotic morphea In rare patients the course is rapid and progressive with multiple enlarging plaques that eventually result in wide-spread involvement of almost the entire skin, except for sparing of the hands and feet (Fig. 43.10). This presentation is referred to as pansclerotic and requires aggressive treatment.

Linear morphea The linear subtype of morphea occurs most commonly in children. In this type plaques develop in a linear pattern, eventually coalescing into a single band of scarring that can extend the length of a limb. When it crosses joints it can cause loss of mobility because of scarring. Linear morphea often involves deeper structures, including muscle and bone. When it involves the scalp and forehead it has been referred to as *en coup de sabre* (Fig. 43.11).

Patients often have a mixed presentation with both linear and plaque types. Several less common forms of morphea have been reported,
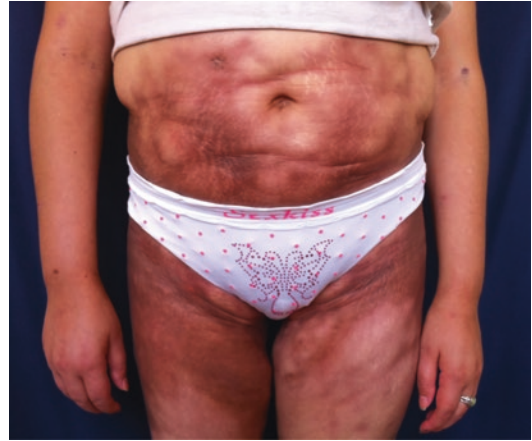
Fig. 43.10 Pansclerotic morphea. Multiple hyperpigmented, atrophic plaques

Fig. 43.11 Linear morphea. Band of scarring on the forehead (en coup de sabre)

including superficial morphea [85], guttate morphea, bullous morphea [86], and keloidal morphea [87, 88].

The diagnosis of morphea is made based on history and clinical examination of the skin. Differentiating from systemic sclerosis is an important first consideration. In contrast to systemic sclerosis, which begins with sclerodactyly, morphea usually does not involve the hands. Raynaud's phenomenon is characteristic of systemic sclerosis and is absent in morphea. Nailfold and serologic findings of systemic sclerosis are not present in morphea. Examination of the genital skin is recommended to detect asymptomatic lichen sclerosus and to direct treatment if present.

The most likely clinical differential diagnoses to consider are eosinophilic fasciitis, lipodermatosclerosis, graft-versus-host disease, and nephrogenic systemic fibrosis (Table 43.8).

Complementary Examinations

Skin biopsy shows an inflammatory pattern of lymphocytes and plasma cells in the dermis and subcutis, and in late lesions thickened collagen bundles are present. The histologic findings may be indistinguishable from those of systemic sclerosis.

Table 43.8 Clinical differential diagnosis of morphea

Systemic sclerosis
Eosinophilic fasciitis
Lichen sclerosus
Lipodermatosclerosis
Graft-versus-host-disease
Nephrogenic systemic sclerosis
Panniculitis
Chemical-induced skin hardening (taxane-induced scleroderma, silicone implant/injection complication, toxic oil syndrome)
Scleredema
Scleromyxedema
Myxedema
Dermatofibrosarcoma protuberans
Cutaneous T-cell lymphoma
Radiation-related skin changes
Carcinoma en cuirasse
Porphyria cutanea tarda

There are no specific laboratory tests to confirm the diagnosis of morphea. Patients with morphea, especially the linear and deep subtypes, often have a positive ANA test. The clinical utility of this test is yet to be determined, and routine testing is not clinically useful.

Therapeutic Approach

For patients with early and limited skin involvement, topical therapy with high-potency steroids, topical calcineurin inhibitors, or calcipotriene is recommended. Patients with continued progression or generalized disease should be treated with either phototherapy (narrowband UVB, broadband UVA, or UVA1) or systemic treatment with either methotrexate or methotrexate combined with pulsed-dose steroids (1 g of Solu-Medrol intravenously daily for 3 consecutive days, repeated monthly for 3–6 months). Systemic therapy should be considered for linear morphea, which often is more aggressive and disabling. An alternative to methotrexate is mycophenolate using doses of 1,000–1,500 mg twice daily [89].

Treatment of morphea is summarized in Table 43.9 [90].

Further progression after a period of quiescence is encountered. Treatment should be restarted in these cases. If the clinical findings are not clear and comparison photographs are not available, a skin biopsy may be helpful. The finding of inflamma-

Table 43.9 Treatment algorithm for morphea

Limited plaque morphea	Generalized morphea (without joint contractures)	Linear morphea (involving the face or crossing joints)
↓ Topical steroids (inflammatory phase)	↓ Phototherapy (NB-UVB, UVA, UVA1)	↓ Methotrexate and systemic steroids
↓ If no response after 4–8 weeks	↓ If no response after 4–8 weeks	↓ If no response after 8 weeks
Topical tacrolimus	Methotrexate and systemic steroids	Phototherapy (UVA, UVA1, NB-UVB)
↓ If no response after 4–8 weeks	↓ If no response after 8 weeks	↓ If no response after 8 weeks
Calcipotriol and betamethasone dipropionate or Topical imiquimod or NB-UVB, UVA, UVA1	Change to mycophenolate mofetil	Change to mycophenolate mofetil

NB narrowband

tion on the biopsy suggests clinical activity and may be compelling to restart therapy.

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Dermatologic Manifestations in Renal Failure

44

Lídice Dufrechou Varela, Alejandra Larre Borges, and Andrea Nicola Centanni

Key Points

- The three most common kidney diseases that lead to end-stage of chronic renal failure (CRF) are:
- Vascular nephropathy
- Obstructive nephropathy
- Diabetic nephropathy

  Of note, the latter is the main cause of CRF in American and Spanish populations [1]

- Most skin disorders are seen in patients undergoing HD, probably owing to the fact that it is the most frequently used renal replacement therapy worldwide [2]
- Skin disorders in chronic renal failure are benign, but almost all of them show a significant impact on the quality of life of affected patients [3, 4]
- The prevalence of dermatoses in chronic renal failure is close to 100% [5–7]

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Introduction

Chronic renal failure (CRF) is a major public health problem worldwide [3]. (It is defined as an abnormality in renal structure or function, with health implications present for at least 3 months. It is classified according to three variables: glomerular filtration rate (GFR), its etiology, and the amount of albuminuria [8].

Administration of kidney replacement therapy is based on the GFR. Patients with GFR less than 15 mL/min should be admitted to a replacement kidney function plan with any of the existing methods [8]. Replacement of renal function is currently performed by three modalities: hemodialysis (HD), peritoneal dialysis (PD), and renal transplant. Most skin disorders are seen in patients undergoing HD, probably because it is the most frequently used renal replacement therapy worldwide since it has been proved to prolong the life expectancy of patients with CRF [2].

The three most common kidney diseases that lead to end-stage CRF are vascular nephropathy, obstructive nephropathy, and diabetic nephropathy. The latter is the main cause in American and Spanish populations [1].

Of note, this chapter does not discuss dermatologic conditions that are common after transplantation in immunosuppressed patients; this information is available in another chapter.

These patients are considered to have a chronic inflammatory status caused by multiple factors, some of which include the underlying disease, a

permanent fistula or catheter, the membranes used for HD or PD, and the drugs and supplements that they receive [9].

From a dermatologic point of view, there is a high frequency of dermatoses associated with this condition. They can be divided as specific and nonspecific, the latter having the highest prevalence, but all of them showing a significant impact on patients quality of life [3].

Skin changes reported in patients with CRF are diverse [3]. Most skin disorders are benign and do not affect the course of CRF [4]. Sometimes skin disorders can predict the initiation of a renal replacement plan, or may be precipitated by it [3, 4].

Epidemiology

Few worldwide publications describe the prevalence and characteristics of skin alterations observed in patients with CRF and in patients receiving HD. Pico et al. (1992) registered a 100% prevalence of skin lesions in patients with CFR while Bencini et al. (1998) reported 79% prevalence [5–7]. In accordance with these studies, Udayakamur et al. (2006) conducted a study of dermatoses in 100 patients receiving HD, for which the prevalence was 82% [5, 6]. We recently conducted a study in Uruguay about the prevalence of dermatoses in 200 patients in HD, which found a prevalence of 98%.

Multiple factors are described to explain the greatest amount of dermatoses affecting patients with CRF, and these are briefly mentioned in Chart 44.1.

Practically, skin changes in CRF are classified into four groups depending on the relationship with the renal disease or the renal treatment, as described in Chart 44.2.

Cutaneous Manifestations of Chronic Renal Failures

From a dermatologic point of view, a high frequency of dermatoses and skin lesions are associated with this condition. For practical

Chart 44.1 Multiple factors described to explain the greatest amount of dermatoses affecting patients with CRF

Factors described to explain the dermatoses affecting patients with chronic renal failure
Skin dehydration (specially epithelial) with malfunction of the eccrine sweat glands [5, 8]
Dysregulation of calcium and phosphorus metabolism [6]
Chronic systemic proinflammatory condition; for patients receiving hemodialysis, postulating the permanent fistula or catheter as a possible active element [4, 6]
Type of hemodialysis membrane used, which is a questionable concept [9]
Urochrome skin storage [4, 11]
Hypovitaminosis D [5, 8]
Hypervitaminosis A [5, 8]
In hemodialysis patients, higher amount of melanocyte-stimulating hormone β because of poor excretion via hemodialysis [12, 13]
Accelerated erythropoiesis [3, 8]
Altered hemostasis, among other factors mostly by high concentration of urea [10, 11]
Heparin use [10, 11]
Protein malnutrition [5, 10]
Altered cellular immunity [5, 14]
Iron deficiency [3, 8]

Chart 44.2 Classification of skin changes in chronic renal failure according to the relationship with the renal disease or the renal treatment [10]

Causes of skin changes in chronic renal failure
The disease itself that is generating the kidney malfunction
Kidney disease itself
Established treatment
Drugs that the patients receive

purposes, these dermatoses can be grouped into nonspecific (with higher prevalence) and specific. All of them have a significant impact on patients' quality of life [9, 14].

Nonspecific dermatoses are listed in Chart 44.3 and the specific dermatoses are in Chart 44.4.

Besides the aforementioned, there exist iatrogenic dermatoses caused by treatment and adverse drug reactions [6, 10].

Xerosis, bruising, and itching are ubiquitous in this population and are considered multifactorial xerosis, pale skin, and itching were the most prevalent findings according to an Indian study

Chart 44.3 Dermatoses grouped as "nonspecific" in chronic renal failure [8, 9, 14]

Nonspecific dermatoses in chronic renal failure
Xerosis
Pruritus
Dyschromia
Ecchymosis
Gynecomastia
Cutaneous infections
Skin cancer
Mucosal alterations
Faneral disorders

Chart 44.4 Dermatoses grouped as "specific" in chronic renal failures [4, 8–10, 14]

Specific dermatoses in chronic renal failures
Acquired perforating dermatoses (APD)
Bullous dermatoses
Calcification disorders
Nephrogenic systemic fibrosis (NSF)
Specific nail changes
Uremic frost

conducted in 99 patients [4, 10, 14]. This correlates with our findings according to a Uruguayan study, conducted in 2015, of dermatoses in 200 patients receiving HD.

Nonspecific Cutaneous Entities with Higher Prevalence in Patients with Chronic Renal Failure

This grouping mechanism is currently considered controversial since these skin changes could be either coincidental or associated with factors other than CRF, such as the etiologic condition causing renal failure [12].

Xerosis

Xerosis, or dry skin, is a common skin disorder described as the most common skin disorder found among patients with CRF, especially in patients receiving regular HD [4, 9, 10]. It is characterized clinically by rough, scaly, and often itchy skin [2]. A frequency between 50% and 70% in patients undergoing HD is reported [4–6, 8, 10, 11].

Pruritus

Pruritus is one of the most distinctive and troublesome symptoms among patients with CRF, but seems to be absent in patients with acute renal disease [5, 6, 8, 10]. A prevalence rate of 50% has been found in different studies [5, 8–10]. Pruritus has been associated with the degree of renal impairment of the patient and is considered an inflammatory systemic disease rather than a skin disorder per se [5, 9, 15]. It may be accompanied by xerosis but there is no direct correlation between these two entities [15].

The prevalence in patients undergoing HD is between 58% and 90% [5, 11, 15, 16].

Various publications describe that severe pruritus improves after HD, others report no improvement, while some describe patients who report its aggravation after starting HD [5, 9, 10, 16]. Pruritus seems to be more severe in patients with diabetes mellitus (DM) [5, 6].

Dyschromia

Two types of pigmentary changes are described: diffuse hyperpigmentation and citrine yellowish tint [5, 6].

Thomas et al. reported that dyschromia occurs in 32% of HD patients while others refer to prevalence between 25% and 75%, this percentage being higher in patients on maintained HD [10]. In our experience, the prevalence was 31.2% in the 200 patients receiving HD studied.

Diffuse hyperpigmentation is a relatively common early sign and is located in sun-exposed areas [14, 15].

Pallor is observed more frequently in patients receiving sustained HD, with an incidence from 40% to 60% reported. It is difficult to quantify and is defined as an unusual lightness of skin color when compared with normal hue [16], it is attributed to chronic anemia and dysfunctional erythropoiesis [3, 8, 12, 13]. For some authors, pallor is a hallmark in patients with CRF and adds significant morbidity. It correlates with the hemoglobin level, presenting higher incidence in patients with levels lower than 8 g% [6].

Ecchymosis

Ecchymosis prevalence varies from 10% to 60% [5, 10, 11]. It is clinically observed as a

subcutaneous lesion characterized by deposits of extravasated blood [16].

Gynecomastia

Gynecomastia has a reported prevalence of 40% in patients undergoing HD [5]. The development of this clinical sign seems to occur 1 or 2 months after starting HD, and spontaneous regression is seen in most cases within a year [17].

Cutaneous Infections

A prospective Indian study of patients undergoing HD reported a prevalence of 26.26% of bacterial, viral, fungal, and parasitic infections, bacterial ones being the most common among diabetic patients [5, 10, 15].

The most common are the fungal infections such as tinea versicolor and onychomycosis; the latter also most prevalent in patients with DM [5, 6]. In Nigeria a high prevalence of tinea versicolor is reported, the predominant location being upper extremities and not in the "classic" areas where sebum production is increased [11].

The most prevalent viral infections reported are warts, herpes simplex, and herpes zoster (VHZ), although in some studies no statistically significant differences were found compared with the general population [5, 7]. Herpes reactivation has been reported more frequently in this population, and supplements with vitamin D and iron have been linked to a lower incidence [18].

Skin Cancer

Immunosuppression in these patients would predispose to higher prevalence of skin cancer, basal cell carcinoma (BCC being) the most frequently reported, although its prevalence has not been compared with that in the general population [5]. In our recent experience the prevalence of BCC and squamous cell carcinoma (SCC) was similar (4% and 4.5%, respectively). One partial possible explanation for the increase in SCC in this study is the fact that we conducted our study in Uruguay, where population is predominantly Caucasian with a high degree of sun exposure as a result of the latitude and social behavior regarding tanning habits. However, in the Uruguayan population BCC is more frequent than SCC. This

would favor skin carcinogenesis in susceptible individuals with low phototypes [19]. This study shows that the relationship between the prevalence of BCC and SCC in the HD population would resemble what happens in renal transplant patients in whom the BCC/SCC ratio is reversed [20] (see Box 44.1).

> ### Box 44.1 BCC and SCC in the HD Population of Uruguay [19]
>
> The authors conducted a study in 2015 about the prevalence of dermatoses in 200 patients receiving hemodialysis. This study allowed the diagnosis of melanoma in two patients, one of them with Breslow thickness of 0.73 mm and the other of 1.3 mm. The reported incidence in Uruguay, where the study was conducted, is 5.2 cases per 100,000 population per year. There are no literature reports on the prevalence of melanoma in hemodialysis patients, this being much higher than that reported in the general population of this country.

Mucosal Alterations

A prevalence of 90% is reported for oral mucous membrane disorders among patients with CRF. Macroglossia ("uremic tongue"), xerostomia, and ulcerative stomatitis are the most frequent findings [5, 10, 21].

Other mucous membrane disorders are angular cheilitis, furred tongue, and uremic breath, the latter being caused by a high concentration of urea in saliva and ammonium degradation [5, 11].

Faneral Disorders

Diffuse hair loss and diffuse alopecia with dull hair are described as distinctive features among patients with CRF [4, 12].

A Brazilian study reported that the prevalence of hair loss and dull hair was between 26% and 33% [11].

Ungular disorders described are koilonychias, subungual hyperkeratosis, onycholysis, Mee's lines (leukonychia transverse bands), Muehrcke's lines (double white cross band),

splinter hemorrhage, absence of lunula, and Beau's lines [5, 22]. The prevalence of these entities, plus Lindsay nails (better known as "half and half nails"), is estimated to be 71.4% of patients with CRF [11, 23].

Specific Skin Entities Characteristic of Patients with Chronic Kidney Disease

The prevalence of these entities has been studied in patients receiving HD, but not in patients with CRF. In a case–control study conducted in Egypt a prevalence of 3% was reported among 128 patients receiving HD [12]. These figures do not match with our previously mentioned study, where prevalence was 14%. This difference could be explained in part by the exclusion in the Egypt study of various dermatoses included in our study, such as fistula dermatoses and Lindsay nails.

Acquired Perforating Disorders

Several perforating disorders have been described in patients with CRF. They can be primary or acquired and include perforating folliculitis, Kyrle's disease, reactive perforating collagenosis, and acquired perforating disorder (APD) [5, 8, 10, 13].

The term APD or perforating disorder in kidney disease is used for the description of follicular hyperkeratotic papules in these patients [5, 13]. APD is an acquired skin disease characterized by transepidermal elimination of dermal material with minimal damage to adjacent structures [5, 7, 13, 14, 19].

The reported incidence among patients with CRF varies between 4.5% and 11% [9, 13, 14]. Higher prevalence is described in patients of African descent and patients with DM [7, 9, 13, 19].

Bullous Dermatoses

Bullous dermatoses in renal failures include porphyria cutanea tarda (PCT), pseudoporphyria, and bullous cutaneous drug reactions. The latter is not specific of patients with CRF. The prevalence of these three entities varies from 1.2% to 18% [19].

Porphyria Cutanea Tarda

PCT is a disorder in heme biosynthesis resulting in vesicles and blister rash on sun-exposed areas [14]. It can be divided into inherited or acquired. In acquired PCT the deficient enzyme is located in the liver [8, 13, 14].

The reported incidence of PCT is in the range of 1.8–3%. It was considered a common condition in patients receiving HD in the pre-erythropoietin era, whereby iron overload was common [8, 9, 13, 14].

In PCT the standard HD cannot remove uroporphyrins. These levels in patients with CRF without PCT are similar to the ones found in PCT patients with normal renal function. Currently PCT occurs in anemic HD patients with erythropoietin resistance that requires red blood cell transfusions. In such patients, treatment is based on reducing iron stores and plasma levels of porphyrins [14, 19].

Pseudoporphyria

Pseudoporphyria is a photodistributed vesicobullous disorder with clinical and histologic features similar to those of PCT but without any biochemical porphyrin abnormalities [8, 13, 14, 19, 24].

Calcification Disorders

Disorders of calcification are a heterogeneous group of diseases whose common denominator is the deposit of calcium. Calcium salt deposits in the skin and soft tissues are known as calcinosis cutis [13, 25]. In the context of a patient with chronic kidney disease it is subclassified as benign nodular calcification (BNC) [14]. When intravascular calcium reservoir occurs and is accompanied by initial fibroplasia, vascular occlusion, and soft tissue necrosis, the diagnosis is calciphylaxis, also known as calcifying uremic arteriopathy [7, 9, 14].

Calciphylaxis is a frequently lethal entity because of progressive skin necrosis secondary to calcification of small blood vessels [9, 13, 14]. BNC and calciphylaxis occur more frequently in patients with CRF. While calciphylaxis is more common in patients with CRF, it has also been reported in other entities such as in renal transplant recipients, Crohn's disease,

cirrhosis, rheumatoid arthritis, inflammatory bowel disease, neoplasms, systemic lupus erythematosus, human immunodeficiency virus (HIV) infection, and primary hyperparathyroidism [13, 14]. Kidney failure is not a requirement for the development of this phenomenon [8, 25].

The overall incidence of calciphylaxis in HD patients is estimated at between 1% and 4%, women being more commonly affected [8, 13].

Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis (NSF) is a systemic condition with prominent cutaneous manifestations encompassed in fibrosing sclerosis-like disorders, observed in patients with renal disease after exposure to contrast agents based on gadolinium during an imaging procedure [14, 26]. It is a chronic and progressive disease without cure [19, 26, 27].

NSF today is well known by dermatologists and nephrologists, being easily recognized by clinical presentation [14, 27]. While most patients suffering from this condition are undergoing HD, it has also been described in patients receiving peritoneal dialysis and those patients receiving HD because of acute renal failure [7, 14, 19, 27, 28]. The estimated prevalence of NSF among patients with CRF is 0.5–6% [26]. The dominant feature is its presentation during kidney failure, both acute and chronic [14, 28].

Specific Nail Changes

Lindsay nails or "half and half nails" is the most frequent ungual alteration in CRF patients, with an approximate prevalence reported in HD patients from 21% to 40% [4, 5, 8, 10, 22]. In the general population the prevalence is 1.4% [5].

Uremic Frost

Uremic frost is one of the most infrequent skin changes that occurs in patients who suffer an acute episode of severe uremia [5, 8]. It was a common finding in the pre-HD era [5, 6].

Dermatoses on the Arteriovenous Shunt

Udayakumar et al. (2006) reported a prevalence of 8% in patients receiving prolonged HD [5, 6].

The authors found three dermatoses of this topography during the examination of 200 patients on HD.

Kaposi's Pseudosarcoma

Few cases are reported of this entity close to the region of an artificially constructed arteriovenous fistula. They are described as purple nodules or plaques that evolve slowly to lilaceous scaly crusted plaques near the fistula [5].

Adverse Drug Reactions

A higher incidence is described in this population, mainly due to the simultaneous administration of multiple drugs and drugs with prolonged half-life [5].

Recent advances in treatment have improved the quality and life expectancy of these patients, resulting in changes in the frequency and characteristics of skin disease [10].

Etiopathogenic Mechanisms

Xerosis

Cutaneous xerosis may be explained as a dysfunction and reduction in size of eccrine sweat glands, suggesting an alteration in the secretion product that results in epithelial dehydration. The high diuretic regime in these patients could also be involved [4–6, 8, 14, 21]. In the study conducted by Udayakumar et al. (2006), 37% of the patients also had associated pillar-like keratosis lesions on extensor surfaces, xerosis being more severe in patients who also had DM [5]. In our experience, xerosis was found in 79.4% of 200 patients receiving HD. These figures coincide with previous studies in Brazil and in the United States [3, 5]. This Uruguayan study researched the relationship between DM and xerosis with no statistically significant data as reported in the Brazilian study, where 72.5% of patients had DM [3].

Pruritus

The etiopathogenesis and pathophysiology of pruritus is complex, since several uremic and

nonuremic factors contribute to its development [5, 10, 25]. In this sense, two hypotheses are described: the immunologic and the opioid hypothesis. The first one is based on considering uremic pruritus as a systemic disease. This idea is based on the proven benefits of the treatment with ultraviolet B (UVB) and thalidomide or calcineurin inhibitor intake such as tacrolimus [9]. UVB radiation attenuates the development of T-helper 1 (Th1) cells for Th2 differentiation, which leads to decreased production of interleukin (IL)-2. In addition, serum levels of proinflammatory markers such as C-reactive protein and IL-6 are increased in CRF patients with pruritus compared with those without pruritus, confirming the inflammatory nature of the condition. Opioid hypothesis proposes that pruritus is part of a change in the endogenous opioid system, overexpressing μ-opioid receptors in dermal skin cells and lymphocytes. This overexpression, with a concomitant decrease of κ-opioid receptors, could cause increased β-endorphin serum in patients with CRF, which would explain the development of pruritus. Use of κ-receptor agonists such as nalfurafine, or naltrexone, a μ-receptor antagonist, improves pruritus in this population [9].

Other possible biological theories proposed to explain pruritus in patients with CRF are urochrome skin reservoir, uremic toxemia, dysregulation of calcium and phosphorus metabolism, proliferation of mast cells with increased levels of histamine, allergy to HD components, and reaction to hypovitaminosis D and hypervitaminosis A [4–6, 8, 10, 11]. Pruritus has been linked to xerosis, although several studies failed to find such a relationship [13]. In HD patients, high plasma histamine levels may be due to allergic sensitization to various components of the HD's membrane and an altered renal excretion of histamine [5, 13]. Parathyroid hormone and divalent ions such as calcium; phosphorus, and magnesium have also been implicated in the pathogenesis of uremic pruritus, since itching is present in severe secondary hyperparathyroidism [5, 7, 10, 19, 29]. The lack of a consistent relationship between levels of parathyroid hormone, calcium, phosphorus, and uremic pruritus indicates that there would be other more important factors involved in the pathogenesis [9, 10, 13, 29]. A study in Brazil revealed a statistically significant correlation between pruritus and elevated levels of phosphorus and magnesium [11]. A Japanese study 1,773 patients in HD identified male gender, high levels of blood urea/nitrogen, β2-microglobulin, hypercalcemia, and hyperphosphatemia as independent risk factors for the development of severe pruritus, whereas a low level of calcium and intact parathyroid hormone were associated with reduced risk [30].

In our experience, factors described in the literature that could influence the presence of pruritus in this particular population could not be proven statistically, including DM, HD membrane type, calcemia, phosphoremia, C-reactive protein level, and intake of vitamin supplements. On the other hand, we emphasize a significant relationship between vitamin D deficiency (in plasma) and the presence of pruritus. Vitamin D deficiency has been linked to pruritus in HD patients [4, 6].

Dyschromia

Diffuse Hyperpigmentation

Pigmentary alterations are attributed to an increase of melanin pigment in the basal layer of the epidermis and superficial dermis, owing to the greater amount of melanocyte-stimulating hormone because of poor HD excretion [12, 13, 25, 26]. Higher prevalence of this entity has been reported in patients who also had positive serology for hepatitis C virus (HCV) [7].

Sallow Skin

Carotenoid, lipochrome, and urochrome deposits in dermal layer and subcutaneous tissue are thought to be responsible for the yellowish sallow dyschromia so characteristic of these patients [3, 12, 13, 27].

Ecchymosis

Ecchymosis is explained by defects in hemostasis, which generate vascular fragility and platelet

dysfunction, to which is added the use of heparin during HD [5, 8, 10, 13]. High concentrations of urea alter platelet aggregation and increase guanidinosuccinic acid levels, which inhibits platelet activity induced by adenosine diphosphate [11].

Gynecomastia

Gynecomastia occurs in the early stages of HD and is explained by a "feedback" after starting treatment. Both in CRF and protein malnutrition, pituitary and testicular function remain suppressed. When protein supplies increases after starting treatment with HD, a second "pubertal" push generates a transient gynecomastia [5, 10]. It has also been attributed to accumulation of prolactin, which inhibits the release of follicle-stimulating hormone and luteinizing hormone, resulting in decreased production of estrogen and progesterone [8].

Cutaneous Infections

HD patients have impaired cellular immunity because of their smaller number of T cells, which could explain the high percentage of infections in this population [9, 14, 15].

Skin Cancer

Patients with CRF receiving HD have been reported have an increased risk of any cancer [31]. Prevalence of skin cancer in CRF patients compared with the general population has not been reported [5]. By contrast, kidney transplant recipients with a higher skin cancer prevalence are well studied, with an SCC-versus-BCC incidence ratio of 3.8:1 and an annual incidence calculated at 6.5%, increasing to 10.5% at more than 10 years post transplantation. Duration of immunosuppression, older age at transplantation, presence of actinic keratosis, male sex, and outdoor occupation are significantly associated with both SCC and BCC in kidney transplant recipients [32]. In transplant recipients, immunosuppressive drugs

severely impair the body's immune functions. Among the cell types affected are T lymphocytes, natural killer cells, and dendritic and other antigen-presenting cells. The end result is disrupted immune surveillance. Thus, a microenvironment is created that is conducive to unrestricted tumor growth [33]. In our opinion, the same situation is likely to occur in CRF patients as this population is considered as being in a chronic immune-suppressed state [5]. As described earlier, this concept agrees with the findings of our study wherein the prevalence of SCC was slightly greater than that of BCC in HD patients. In addition, this population is at greater risk for developing virus-induced neoplasms.

Nonmelanocytic skin cancer behaves more aggressively in chronically immunosuppressed individuals. The exact mechanism whereby this aggressive phenotype is achieved remains elusive [33].

Faneral Disorders

Dull hair is believed to be due to decreased secretion of sebum [5, 10]. On the other hand, all abnormalities in the hair are considered as related to the administration of heparin, hypervitaminosis A, accumulation of toxins, iron deficiency, and drugs frequently used in HD patients such as β-blockers, methyldopa, cimetidine, allopurinol, and indomethacin [11].

Acquired Perforating Dermatoses

The pathophysiology of APD remains unclear at present, although removal of transepidermal material is thought to be the final pathway. One of the most accepted theories explains the phenomenon as resulting from diabetic microangiopathy that would prevent proper healing; however researchers have recognized that this theory cannot explain cases of APD in patients without DM [13, 14]. It is suggested that minimal trauma such as scratching triggers tissue necrosis and that the necrotic material is removed by transepidermal elimination [14, 19]. This theory is supported by

the fact that lesions exhibit the Koebner phenomenon several times. Saray et al. reported that among 11 patients with coexistent APD and DM, none developed lesions of APD until nephropathy occurred. Other authors propose that the underlying renal disease would be the cause of skin diseases; while other another described that the dermal material is a foreign body reaction to an unknown dermal substance [15].

Bullous Dermatoses

Porphyria Cutanea Tarda
From a pathophysiologic point of view, porphyria is caused by enzyme deficiency related to heme biosynthesis, resulting in blocking heme synthesis and the subsequent accumulation of toxic porphyrins. In PCT the deficient enzyme is uroporphyrinogen decarboxylase, which causes the accumulation of porphyrins, especially water-soluble uroporphyrin, in both liver plasma and skin. The skin porphyrin deposit causes oxygen free radicals when exposed to UV radiation, resulting in photosensitivity, blistering, and scarring. Iron plays an essential role in the development of symptoms of PCT because this metal encourages early enzymatic function for the synthesis of heme and inhibits the already poor decarboxylase uroporphyrinogen. Moreover, iron promotes the oxidation of the porphyrin precursors [14]. In PCT the standard HD cannot remove uroporphyrins [14, 19].

Alcohol, estrogens, HCV, hepatitis B virus (HBV), and HIV are thought to precipitate further uroporphyrinogen decarboxylase dysfunction, possibly through an iron-dependent mechanism [8, 9, 14, 19].

Pseudoporphyria
Pseudoporphyria can develop as a consequence of photosensitizing drugs (including naproxen, furosemide, nalidixic acid, bumetanide, tetracyclines, and amiodarone), excessive exposure to ultraviolet A (UVA) (in the case of tanning beds), or CRF without another precipitant factor. It is more likely to occur when other precipitants are present in a patient receiving HD, such as photosensitization [8, 13]. The mechanism of induction is unknown [14].

Proposed factors that may elicit pseudoporphyria in a patient with CRF and receiving HD include diuretics, aluminum hydroxide, polyvinyl chloride HD tubing, hemosiderosis, silicone particles, erythropoietin, and susceptibility to oxygen free radicals. Keczkes et al. (1976) described five patients with CRF who had bullous dermatoses, all of whom were taking furosemide. The causal role of erythropoietin is discussed because many cases of pseudoporphyria were reported before its use. In addition, through reducing iron stores, it can alleviate pseudoporphyria. Possible aggravating circumstances in some of the case reports of peritoneal dialysis-associated pseudoporphyria include probable HVC infection and the use of nifedipine, a known photosensitizer [34].

Disorders of Calcification

Benign Nodular Calcification
The factors that predispose to such calcification include an increase in calcium and phosphorus products in serum, the degree of secondary hyperparathyroidism, the level of magnesium in plasma, the degree of alkalosis, and the presence of local tissue injury [35].

Calciphylaxis
The pathophysiology of this entity is complex. It is believed that calciphylaxis is the result of an imbalance between inductors and inhibitors of calcification in the vascular wall [8]. The Braun model is practical and divides homeostasis of calcium and phosphorus metabolism into five systems: intestine, kidney, bone, intravascular compartment, and extraosseous calcifications. The only way of removing excess phosphorus in patients with CRF is bone deposition, osseous calcifications, or removal by dialysis. HD removal is insufficient to prevent phosphorus buildup, even with efficient treatment to reduce intestinal absorption. From the aforementioned, extraosseous calcification is a possible consequence [14].

There are increasing reports that support the relationship between bone and vascular calcification. Elevated levels of uremia and phosphatemia cause transdifferentiation of vascular muscle stem cells into osteoblast-like cells [9, 14].

It is concluded that calcium deposit in vascular walls is a dynamic process and not simply due to a passive mineral precipitation secondary to high levels of phosphorus/calcium. There are multiple case reports on patients with calciphylaxis who have normal levels of phosphorus/calcium and normal levels of parathyroid hormone [14, 25].

Calciphylaxis has been linked to acute coronary events. Although calcium deposits generate progressive narrowing of the lumen, the essential event is a thrombotic vascular occlusion [14].

Several risk factors have been linked to the development of calciphylaxis, such as renal failure, female gender, obesity, DM, liver disease, use of systemic corticosteroids, intake of coumarin anticoagulants, serum levels of aluminum higher than 25 ng/mL, hyperparathyroidism, vitamin D exposure, lymphomas, HIV, local trauma, use of calcitriol, salt intake, and production of calcium/phosphorus greater than 70 mg/dL^2 [7, 9, 13, 14, 19]. A series by Dauden Tello et al. (2002) based on 17 patients with cutaneous vascular calcification observed that a large number of patients had hypertension and/or DM and/or atheromatous disease [25].

Nephrogenic Systemic Fibrosis

It is considered that myofibroblasts are involved in this disease, suggesting that certain cytokines, such as TGF-β, could mediate fibroblast proliferation [9, 14, 27].

The etiology is not fully clarified, although exposure to gadolinium (contrast agent) is recognized as an inducing factor of NFS. The lesions appear after approximately 16 days from gadolinium injection [8, 9, 14]. The US Food and Drug Administration (FDA) has created a warning indicating that exposure to gadolinium in patients with renal GFR less than 30 ml/min/1.73 m^2 increases the risk of NSF [9, 14]. This also applies to patients with acute renal failure of any severity associated with hepatorenal syndrome or patients in the perioperative liver transplantation period [14].

Gadolinium is a metal that attracts magnetic forces, making it optimal as magnetic resonance imaging and angioresonance contrast [9, 14]. In its free form it is very toxic to tissues, and combines with chelating agents to create a relatively stable inert compound [14, 26]. After being formed this complex rapidly reaches equilibrium between interstitial and vascular spaces [14].

In patients with normal renal function, 95% of the gadolinium complex is excreted in the first 24 h post administration [9, 14]. In patients with impaired renal function, the removal declines. However, its small molecular weight allows it to be removed via HD up to 95% after three sessions of HD. Current theory suggests that the greater permanence of gadolinium in tissues of patients with CRF allows cytokine signals to activate fibrinogen [14]. The type of gadolinium also appears to be significant [14, 19].

Most cases were exposed to gadodiamide [14, 26]. The challenge is to understand why most patients exposed to gadolinium contrast agents are saved from this entity [14, 19].

Recent surgery, vascular procedures, hypercoagulable states, and thrombotic events have been cited as associated conditions in patients, suggesting that endothelial damage may be a cofactor. High doses of erythropoietin could be a cofactor but without consistent scientific basis [9, 14]. Kidney transplant failure and later onset of HD has also been described as a risk factor [9].

Lindsay Nails

The pathogenesis of this condition is attributed to an increased capillary density in the bed. On the other hand, Lindsay nails are thought to be due to a collapsed venous return in the nail bed [4, 8, 10, 19].

Uremic Frost

Uremic frost due to eccrine deposits of urea crystals on the skin surface in patients with severe

uremia [5, 13, 33]. Evaporation of sweat with high urea concentration causes urea to crystallize and deposit onto the skin [36].

Clinical Presentation

Nonspecific Cutaneous Entities with Higher Prevalence in Patients with Chronic Renal Failure

Xerosis

The term xerosis is often used to refer to the concept of dry skin [2]. It is a permanent symptom in CRF patients, with a clinical picture characterized by dry skin appearance, marked scaling and roughness, and poor skin smoothness (Fig. 44.1). Xerosis often affects the entire surface of the body, and may be more intense in some areas. Severe involvement of certain areas, such as the hands and feet, leads to possible functional impairment. As a consequence of an alteration in the cutaneous barrier function, the skin is more easily exposed to external attacks and aggression. As in some other severe xerotic conditions, a greater susceptibility to irritation caused by chemical factors (e.g., soaps and detergents) may be observed [37]. Severe xerosis can lead to fissured and cracked skin [1].

Pruritus

Itching can be localized or generalized, with the back being the most commonly affected site. The intensity and distribution of pruritus may vary significantly over time [16]. It can occur without skin lesions, being a subjective symptom of the patient (better known as pruritus sine materiae), or become clinically present with lesions such as excoriations, lichen simplex, nodular prurigo (see below), or keratotic papules, all resulting from scratching [21]. Variations are described in frequency and severity and often are associated with severe paroxysms that disrupt sleep and impair the quality of life and daily activity [9, 13, 19]. It also contributes to the occurrence of the Koebner phenomenon of APD [13, 19].

As previously stated, prurigo could be a clinical presentation of pruritus. Nodular prurigo is chronic relatively frequent dermatoses among CRF patients. Hyperkeratotic pruritic papular nodules often develop in a symmetric distribution over extensor surfaces of extremities, and may affect the trunk and buttocks. Lesions become hyperpigmented over time and are often excoriated by scratching. The face and palmoplantar region are usually spared [38, 39]. It is the most intense form of lichenification. Itching is the key symptom, being intense and intolerable with nighttime exacerbations. Evolution is chronic and with no tendency to heal [39] (Fig. 44.2).

Dyschromia

Diffuse Hyperpigmentation

Most cases of diffuse hyperpigmentation are reported in sun-exposed areas and in fewer

Fig. 44.1 Cracked skin and xerosis of the limb

Fig. 44.2 Nodular prurigo

Fig. 44.3 Difuse hyperpigmentation in sun exposed areas

Fig. 44.4 Several ecchymosis of the arm

patients, with hyperpigmented macules on palms and soles [4, 5, 8, 10] (Fig. 44.3).

Sallow Skin

CRF patients may experience sallow complexion or citrine-colored skin, which may present an unhealthy and tired appearance. It occurs mainly as a result of urochrome accumulation in the skin because the impaired kidney cannot function well on its elimination [7, 19, 25].

Ecchymosis

Ecchymosis is characterized by a reddish or bluish macule. The onset of reddish or bluish discoloration of the skin is due to the escape of blood from ruptured blood vessels into the capillaries. It is a subcutaneous nonpalpable purpura. In CRF patients it appears more frequently in regions of trauma, such as arms or legs [13, 14]. It is easily recognized in puncture sites [14, 15] (Fig. 44.4).

Skin-Specific Entities Characteristic of Patients with Chronic Renal Failure

Acquired Perforating Dermatosis

APD is clinically characterized by conical papules with keratotic plugs; the presence of keratotic pits on palms and soles is also described [5, 9, 14]. It predominates in areas of high surface friction or trauma, such as extensor surfaces (most commonly in lower limbs), areas with high density of pilosebaceous follicles,

and the trunk [5, 13, 14, 19] (Fig. 44.5a, b). Etiopathogenically, the constant skin trauma due to pruritus could be the promoting factor [5]. The Koebner phenomenon can be seen [14]. In Caucasians, these papules acquire a pink color while in high phototypes they are brown or hyperpigmented [13, 14]. The most common symptom is severe itching [14]. A minority of patients report pain [13, 14]. The natural evolution is spontaneous resolution of individual lesions with the continuous appearance of new lesions [13].

Porphyria Cutanea Tarda

The clinical presentation does not differ from the one seen in sporadic PCT and is characterized by the development of vesicles and blisters in photo-exposed areas, with a higher prevalence in back of hands and forearms. The presence of scabs and the erosions resulting from trauma are frequently seen, while hyperpigmented scars and milia formation are characteristics in the evolution. It is also common to see subtle face hypertrichosis and hyperpigmentation in sun-exposed areas. Bright, depressed, and slightly infiltrated plaques, known as sclerodermiform plaques, can be observed [8, 9, 13, 14].

Pseudoporphyria

Clinical features are identical to those of PCT but without hypertrichosis, hyperpigmentation, or sclerodermiform plaques [8, 13, 14] (Fig. 44.6).
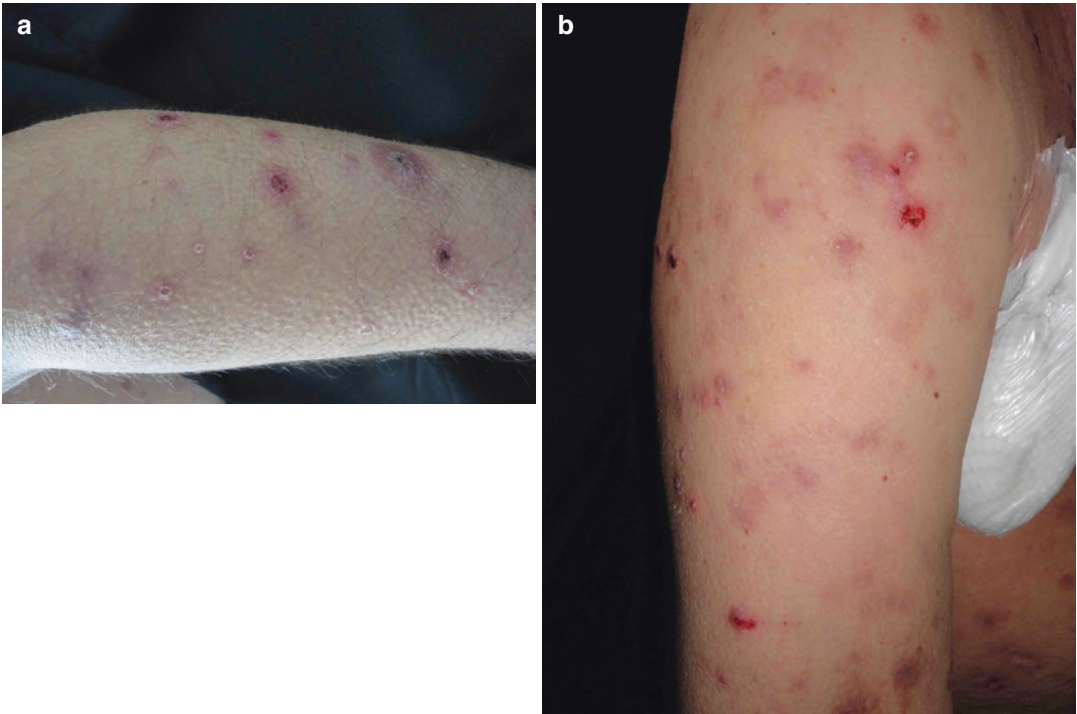
Fig. 44.5 (a, b) Acquired perforating dermatosis

Fig. 44.6 Erosions due to blisters, pseudoporphyria

Benign Nodular Calcification

Also known as calcinosis cutis, this condition presents clinically as papules, plaques, or nodules near joints or fingertips firm to palpation. Most lesions are asymptomatic, although when located in the aforementioned topographies they can compromise joint function and be painful. In some lesions, the output of thick whitish substance can be seen through the skin [8, 14] (Fig. 44.7).

Calciphylaxis

Calciphylaxis is a life-threatening affection that presents acutely by invalidating and severe cutaneous pain. The skin initially shows a small area of erythema or livedo reticularis (retiform purple) that rapidly progresses to shallow or deep stellate ulcerations, with central necrosis or sloughing. In peri-ulcer areas, skin becomes purple with a livedoid pattern on which patients experience exquisite pain [7, 8, 14]. It presents distinctive distribution features that could predict prognosis. Distal acral involvement has a better prognosis than proximal involvement. Peripheral pulses are

preserved distal to necrotic areas. When also involved with myopathy, hypotension, fever, dementia, and injury to the central nervous or intestinal system, it is known as systemic calciphylaxis [7, 8, 13]. Ocular ischemic neuropathy commitment has been described [7].

Nephrogenic Systemic Fibrosis

The clinical presentation of NSF is progressive, symmetric, and characterized by skin hardening of extremities and trunk, commonly being described as orange peel or woody induration and reminiscent, in some aspects, of scleromyxedema [5, 8, 14, 19, 26].It firstly shows a clear erythematous papule that may associate with edema of the affected region and then coalesces into brownish indurated plaques at distal areas, generally in the lower limbs, progressing in a cephalic fashion [7, 14, 26]. Sclerosis can generate joint contractures accompanied by numbness, itching, or pain [9, 14, 19, 26]. It tends to spare the head and neck [14]. Latterly, patients develop epidermal atrophy and loss of hair with orange cobblestone peel and hyperkeratosis with pruritus [9, 26]. Some extracutaneous manifestations include yellowish plaques in the sclera, muscle weakness, and deep rib or hip pain [8, 14, 26]. Although progress is slow, a minority of patients may suffer an acute course with immobility lasting several weeks [14].

Lindsay Nails

Lindsay nails are a change on the coloration of the nails characterized by red or chestnut coloration in its distal half (not disappearing with pressure) and white in its proximal half [5, 8, 15, 19]. Both fingernails and toenails are affected [19, 22] (Fig. 44.8a, b).

Uremic Frost

Uremic frost consists of a white-yellowish crystal-like cover, formed by urea in the beard area and other parts of the face, neck, and trunk. In 2 weeks peeling occurs and fissures appear [5].
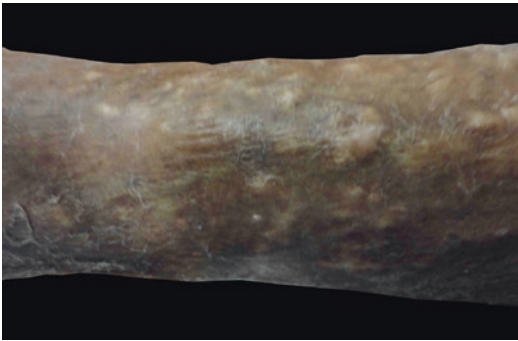
Fig. 44.7 Benign nodular calcification

Complementary Examinations

Most of the aforementioned dermatoses do not require complementary examinations to reach diagnosis. Dermatoses that do require complementary examinations are cited here.
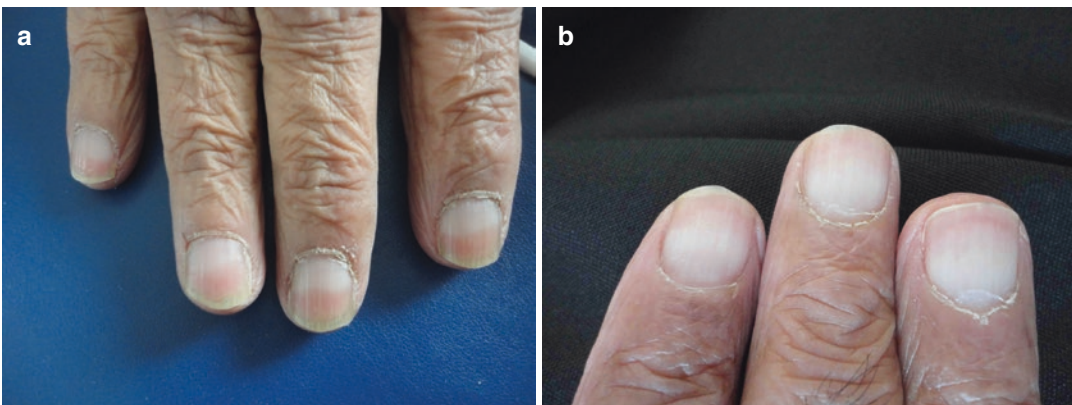
Fig. 44.8 (**a**, **b**) Lindsay nails

Acquired Perforating Dermatoses

Skin biopsy can help to diagnose this entity in most cases [14]. Differential clinical diagnoses include primary perforating disorders, nodular prurigo, eruptive keratoacanthomas, phrynoderma (vitamin A deficiency), hyperkeratotic lichen, and warts [8, 13, 14].

Histopathology is similar to that of other perforating dermatoses, and overlapping characteristics can be observed in the same skin biopsy sample [8, 13, 14]. An accumulation of keratin is typically observed to fill an epidermal invagination or a dilated hair follicle [8, 14, 19]. The adjacent dermis is characterized by altered and thickened collagen fibers and/or elastic fibers [9, 14]. In evolved lesions, giant foreign body cells due to degenerating inflammatory cells can be seen [8, 13].

Porphyria Cutanea Tarda

Patients with PCT have a large iron reservoir, so high levels of iron and ferritin support this diagnosis. The presence of high levels of urine uroporphyrin I and low urine levels of uroporphyrin III, 8-carboxyl uroporphyrin, and 7-carboxyl uroporphyrin are sufficient for diagnosis. In anuric patients, assessing the stool for high levels of isocoproporphyrin III and plasma for high levels of uroporphyrin may be used to reach diagnosis [14].

Skin biopsy for histopathology and direct immunofluorescence helps to distinguish PCT and pseudoporphyria from other subepidermal bullous dermatoses [14].

Histopathologic findings are subepidermal separation with minimal or no swelling. It is typical to find collections of intraepidermal eosinophilic collagen type IV, called caterpillar bodies, in the basement membrane. Direct immunofluorescence of perilesional skin reveals linear deposits of IgG, complement 3, and fibrinogen along the dermal–epidermal junction and around blood vessels [8, 13, 14].

Serology for HIV, HBV, and HCV should be considered, as well as genetic testing for hemochromatosis in all patients with PCT as they are frequent comorbidities and triggers of this disease [14].

Pseudoporphyria

As already described, porphyrin assays show normal plasma and fecal levels. Biopsy of affected skin reveals subepidermal blisters, lymphocytic perivascular infiltrate, and sclerosis of collagen. In other words, histopathologic features are similar to those of PCT although less thickening of the vessel wall is observed [8, 13, 24]. Direct immunofluorescence may be positive, showing linear IgG deposits in vessel walls and at the basement membrane zone. These results are consistent with a diagnosis of HD-associated pseudoporphyria [24].

Difficulty often arises in establishing a diagnosis of pseudoporphyria in patients undergoing HD because PCT concurrent with CRF may occur. Patients without symptoms undergoing long-term HD have been shown to exhibit higher plasma uroporphyrin levels than normal controls, further complicating the distinction between pseudoporphyria and true PCT. These levels have reached those measured in the plasma of patients with symptomatic PCT. Interestingly, uroporphyrin concentrations are significantly higher in patients undergoing HD in comparison with patients undergoing continuous ambulatory peritoneal dialysis, possibly because of better clearance of larger molecular weight "middle molecules" such as uroporphyrin by continuous ambulatory peritoneal dialysis [34].

Investigation of the dialysis patient poses practical diagnostic difficulties because urinary porphyrin profiles are not available. It is important to investigate anuric patients with fractionation of both fecal and plasma porphyrins [40].

Benign Nodular Calcification

A skin biopsy should be performed to confirm the diagnosis of BNC. Histopathologic calcium reservoir is shown in dermis and subcutaneous

tissue. Foreign body giant cells and inflammation can be seen around calcium deposits. Although calcium is clearly distinguishable with hematoxylin and eosin staining, Von Kossa staining (calcium stains black) can highlight deposits [8, 14].

The degree of severity is related to calcium and phosphorus levels in plasma. Normalization of the aforementioned minerals can lead to regression of lesions [8].

Calciphylaxis

Skin biopsy may confirm this entity, although histologic findings are not pathognomonic [8, 13, 14]. Diagnostic features are located in the deeper dermis and subcutaneous tissue, so biopsy should be deep. The distinctive features of intimal hyperplasia and medial calcification are located in dermal small arterioles or subcutaneous arteries and arterioles. Fibrin thrombi in the vascular lumen of dermis and subcutaneous tissue are frequently observed. Overlying dermis and epidermis are necrotic and ulcerated [8, 9, 13, 14]. A few calcium deposits around lipocytes or global calcification of subcutaneous tissue capillaries may be observed [13].

X-ray of the affected area shows the medial calcification as a double reticular fine line in the vessel topography. The commitment of small vessels is radiologically defined as involvement of smaller vessels than 0.5 mm in diameter and is probably the most specific radiologic finding of calciphylaxis. Mammography is more sensitive in many cases, though not routinely performed [13].

The differential diagnosis can be divided into processes of connective tissue such as vasculitides, hypercoagulable states (cryoglobulinemia), deep fungal infection and, on the other hand, embolic events [13, 14]. The crucial point in diagnosis is an adequate sample of tissue for biopsy [14].

Laboratory analysis includes renal function, phosphorus, calcium, parathyroid hormone levels, and urine sediment. Antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody tests may also be necessary. Cryoglobulins and serology for hepatitis are usually requested [13, 14].

Nephrogenic Systemic Fibrosis

Differential diagnosis in these patients includes other fibrosing disorders such as scleromyxedema, sclerederma diabeticorum, and diffuse or limited cutaneous sclerosis [19, 26]. One of the features that differentiate these entities from NSF is the absence of facial involvement in the latter [9, 26]. The absence of Raynaud's phenomenon, periungual capillary dilation, and telangiectasia also excludes other sclerotic disorders [26].

Negativity of antibodies in plasma helps to rule out autoimmune sclerosis, and the absence of circulating paraprotein helps differentiate the NSF from scleromyxedema [26–28].

Gadolinium has been quantified in skin biopsies from patients with NSF. It has been described as 35–100 times higher bone deposits compared with healthy volunteers [14].

The histopathologic features mimic scleromyxedema and depend on the evolutionary stage of the lesion biopsied [5, 14]. The older lesions show CD34, procollagen 1, and CD45Ro in fusiform dermal cells with varied amount of mucin [7, 14]. The expression of CD34 and procollagen 1 suggest that the fusiform dermal cells are circulating fibrocyte infiltrates [14, 19]. The presence of dense fibrous bands that extend into the subcutaneous tissue is related to the clinical presentation of cutaneous induration [14]. Inflammation is absent [9, 14].

Therapeutic Approach

Some of the mentioned dermatoses tend to disappear when the patient is subjected to renal transplant, confirming the role of renal dysfunction in the onset and perpetuation of these disorders [2].

Xerosis

Dry skin affects patients' quality of life, especially when the hands are involved [2]. Treatment is based on skin hydration and treatment of pruritus, if present. Repetitive bathing must be avoided should be short, with warm water avoiding

friction with sponges [2, 21]. Once bathing is over, immediate application of emollients preventing transcutaneous water evaporation is mandatory. The application of creams, ointments, or scented lotions is not recommended (especially if they contain alcohol) [2].

The most widely used and effective humectant is glycerol, owing to its excellent hygroscopicity, lipid-modulating, and corneodesmolytic activity. Other humectants include urea and NMF (normal moisturizing factor) components, whereas other corneodesmolytic agents include the hydroxyacids. Topically applied ceramides and other bilayer-forming lipids are, therefore, an option. An equimolar mixture of the three dominant stratum corneum lipids (ceramide, cholesterol, and fatty acids) has been shown to allow normal rates of barrier recovery, whereas adjustment to a 3:1:1 molar ratio accelerates barrier recovery [41].

Pruritus

Despite the almost constant presence of xerosis, classic emollients and keratolytic and antihistamine therapies produce modest benefit in the treatment of pruritus [7, 13]. Antihistamines have limited benefit in uremic pruritus and relies on its side effect to induce drowsiness [9]. Renal transplantation is seen as curative treatment by some authors [13, 19].

In patients undergoing HD, the type of membrane used does not seem to influence the incidence of pruritus, although an uncontrolled study showed a significant reduction when HD was performed with high-flux membrane polymethylmethacrylate [9]. Some authors believe that general measures in the management of pruritus include optimizing the efficiency of HD using biocompatible membranes and improving the nutritional status of the patient [9, 11, 19].

Topical treatments, besides emollients, include capsaicin cream and tacrolimus. Capsaicin is a natural alkaloid found in the hot pepper plant. It acts by reducing levels of substance P in type C sensory cutaneous nerves. The studies carried out show that applications of 0.025% cream significantly relieves itching in HD patients, with no observed adverse effects. While this is a good choice in localized pruritus, it is impracticable in generalized pruritus [9, 42].

Topical tacrolimus is a calcineurin inhibitor that works by blocking the differentiation of Th1 cells, thereby inhibiting the production of IL-2. There is a single pilot study of 25 patients with uremic pruritus receiving tacrolimus ointment 0.03% for 3 weeks and 0.1% for the next 3 weeks, describing a significant reduction of pruritus without detection of serious toxicity [9]. Since 2006, the FDA has included a warning sign on tacrolimus boxes informing about the risk of cutaneous malignancy after using this agent for long periods. However, to date they have not observed an excessive amount of cutaneous malignancy in 9,800 patients with atopic dermatitis using tacrolimus 0.03% [19].

UVB (280–315 nm) radiation is the most effective treatment for uremic pruritus [8, 13, 19]. The mechanism of action is speculative and is thought to be due to a "photoinactivation" of pruritogenic substances and histamine-releasing factors. UVB also reduces vitamin A levels in the epidermis, which is suggested to contribute to pruritus [5, 13]. Three weekly sessions should be held for several months to obtain benefits. The potential carcinogenic effect of UV radiation requires serious consideration, particularly in patients with Fitzpatrick skin type II or I [9, 19]. Benefits of UVA phototherapy are controversial [7, 13, 19].

Other treatment options include oral cholestyramine, coal, and opioid agonists such as naltrexone or nalfurafine [5, 8]. The latter is successfully used in intractable pruritus in patients receiving HD, based on the hypothesis that endogenous opioids contribute to the development of pruritus. Among various trials the results are controversial [5, 9, 13]. Coal is widely used in England (where phototherapy is a less common treatment modality) as first-line treatment. Six grams daily of activated carbon is used orally and is believed to act by binding pruritogenous substances in the intestinal lumen with absorption preventing action [7, 13]. A limitation of coal is its low tolerance [7]. Cholestyramine, used in other pathologies with high effectiveness,

seems not to show similar efficacy in uremic pruritus. The administration of 5 g every 12 h orally is not well tolerated because of gastrointestinal side effects. The risk of acidosis should be considered [19].

Erythropoietin treatment relieves itching in some HD patients by reversibly decreasing plasma histamine levels, according to a small crossover placebo-controlled study that was carried out for 10 weeks in patients receiving HD [5, 9, 19]. Other drugs that have been tested in uremic pruritus are ondansetron orally (a serotonin antagonist receptor and a selective 5-HT$_3$ antagonist) and gabapentin orally, both with good results [5, 7, 19]. Gabapentin at a dose of 100–300 mg is administered after each HD, reducing significantly the severity of pruritus [9, 19]. Neurotoxic side effects such as dizziness, drowsiness, and coma should be considered. In a small uncontrolled study the efficacy of granisetron (another 5-HT$_3$ antagonist) was shown in uremic pruritus [9].

Thalidomide is a suitable drug for uremic pruritus. It is contraindicated in women of reproductive age because of its teratogenic effect, and must be borne in mind as a possible cause of severe polyneuropathy [7, 9].

A controlled double-blind placebo study showed that nitroglycerin, a dopamine receptor and partial α-adrenergic blocker, at doses of 30 mg per day orally plus 5 mg intravenously in HD relieved pruritus in most patients with an effect lasting 24–48 h [19].

Alternative medicine, principally acupuncture, was reported to be useful in several case reports [7].

Pruritus has a substantial effect on the quality of life of this population, causing discomfort, anxiety, depression, and sleep disorders. The latter is associated with chronic fatigue with impaired physical and mental capacity [9, 19].

Dyschromia

Diffuse Hyperpigmentation

Hyperpigmentation, which commonly affects dark-skinned individuals, is often challenging to treat. It has been demonstrated to have a negative impact on quality of life [43].

To date, specific studies on the treatment of diffuse hyperpigmentation in patients with CRF have been lacking. In any event it appears that treatments tend to be ineffective and disappointing. One possible option is tyrosine inhibitors such as hydroquinone, arbutin, aloesin, azelaic acid, kojic acid, licorice extract, proprietary oligopeptide products, phenylethyl resorcinol, mequinol, and free radical scavengers (α-lipoic acid and ascorbic acid) [43, 44].

Hydroquinone is available in strengths up to 4%, with higher concentrations available as a compounded product. Even with diligent application, hydroquinone takes 3 months or more to produce clinical results, and contact dermatitis is often reported. Combining hydroquinone with another product, such as glycolic acid, vitamin C, or vitamin E, may improve efficacy and shorten the time necessary to achieve visible results. A well-known formula is to compound it with a topical retinoid and corticosteroid. Arbutin is a naturally occurring derivative of hydroquinone that also exerts its antimelanogenic activity via tyrosinase inhibition [43].

On the other hand, melanosome transfer inhibitors such as soy-based products, niacinamide, glycolic acid, and cell-turnover inducers are described. The latter are retinoids, commonly used as monotherapy or in combination with other topical medications. Retinoids have a dual mechanism of action; apart from melanosome transfer they stimulate cell turnover, discarding melanized keratinocytes [43, 44].

Currently laser treatment is a reasonable option for the treatment of hyperpigmentation. Among these, good results are described with Q-switched alexandrite laser, Q-switched Nd:YAG 1064/532 nm, and Q-switched ruby laser [45, 46].

Medical makeup, transitory or definite, is an interesting option for the management of hyperpigmentation. Last but not least, external photoprotection is fundamental to the hope of improving hyperpigmentation, whatever its etiology. Sun exposure always plays an aggravating role, considerably reinforcing hyperpigmentation

already present and facilitating the appearance of new brown areas [47].

Sallow Skin

To the best of our knowledge there are no published reports to date of cosmetic treatments performed for this type of dyschromia.

Acquired Perforating Disorder

There have been no randomized controlled trials comparing different treatment modalities [13, 14]. There are reported cases of spontaneous resolution [19, 48]. High-potency topical corticosteroids under occlusion and intralesional corticosteroids could collaborate to reduce swelling and itching but do not prevent the appearance of new lesions [7, 8, 14]. Topical and oral retinoids, and oral vitamin A (100,000 U/day) have also been reported as having some therapeutic success, in addition to cryotherapy and topical keratolytic drugs [7, 8, 10, 13, 14, 49]. Kidney transplantation has shown benefits in some cases, although cases of APD after transplantation have been described [9, 14, 19]. A recent report has documented therapeutic success with five patients who were treated with narrowband UVB two or three times per week. Pruritus improved after three to five sessions and smaller lesions began to return after five to seven sessions. A maintenance dose of one or two times per week slowed the development of new lesions for at least 7 months in two of the five patients reported. There are isolated cases mentioning improvement with allopurinol (100 mg/day) and allopurinol combined with psoralen and UVA [3, 28, 48, 49].

Porphyria Cutanea Tarda

As mentioned earlier, standard HD does not remove porphyrins; however, high-flux membranes have led to their reduction, though generally not sufficient to generate clinical remission [8, 9, 13, 14].

Avoidance of sun exposure is a crucial factor in treatment [9]. The mainstay of treatment in patients with normal renal function is based on phlebotomy of 500 mL every 2 weeks, a procedure not feasible in patients with CRF [8, 13, 14]. Chronic kidney disease patients with iron overload and currently not requiring blood transfusion can be treated with small-volume phlebotomy (50–100 mL) once or twice a week. This regime has been reported to induce remission after 8 months of treatment. The normalization of iron and ferritin levels is the ultimate goal of treatment [14].

Chloroquine acts by binding to porphyrins, chelating them and facilitating their excretion. Attempts to remove this complex via HD have been unsatisfactory and may result in an exacerbation of the disease, and for this reason chloroquine is not fully recommended [14, 19].

Deferoxamine has been used as an iron and aluminum chelator in toxicity cases. Several researchers have used this drug in HD patients with PCT, obtaining discordant results depending on the administered dose [8, 14]. More recently another oral-administration iron chelator, deferasirox, is available, with no reported use in patients with PCT [14].

IFN-α treatment has shown to induce remission, suggesting that HCV could play a role in PCT [19].

Benefits of plasma exchange have also been shown, by removing 4 L of plasma twice and separated for 48 h, and reconstruction of erythrocytes with fresh frozen plasma [19].

Complete remission has been reported in patients after receiving a kidney transplant [14].

In every case the withdrawal of precipitating factors such as alcohol, exposure to sunlight, and estrogens is essential [13, 14]. Suspension of iron supplements and vitamin B is highly recommended [9].

Pseudoporphyria

The cornerstone of treatment is based on discontinuation of the suspected photosensitive drug and UVA strict protection [8, 14, 19]. There are increasing numbers of reported cases of pseudoporphyria associated with HD, with complete remission following

treatment with *N*-acetylcysteine. The dose ranges from 800 to 1,200 mg per day divided into two doses. It is believed that *N*-acetylcysteine increases production of glutathione, a powerful antioxidant. The improvement mechanism is not clear. However, double-blind controlled studies should be performed to confirm its effectiveness. Even with proper treatment, the symptoms take months to subside [14, 19].

Benign Nodular Calcification

The therapeutic goal is to normalize calcium/phosphorus levels, thereby achieving cure by spontaneous disappearance of lesions [14]. An antacid recently approved (sevelamer), an organic phosphate binder, is recommended as the one of choice [13]. In refractory cases surgery may be considered [13, 14].

Calciphylaxis

Treatment of patients with calciphylaxis is frustrating, with mortality rates of between 60% and 80%. Sepsis remains the leading cause of death [8, 13, 14].

Calciphylaxis prevention is achieved by minimizing risk factors such as obesity, local trauma, calcium/phosphorus intake control, avoidance of excessive vitamin D administration, and secondary hyperparathyroidism [13, 14, 19]. Relieving pain is essential in the therapeutic management of these patients [19]. Most current therapeutic options aim at calcium/phosphorus metabolism disturbances, a diet low in phosphorus (<43 mg/day) being a main therapeutic [7, 9, 13, 14]. Bisphosphonates such as sevelamer have been reported anecdotally as effective, but the overall prognosis is poor. Parathyroidectomy in patients presenting with hyperparathyroidism has shown controversial results, although it has shown some efficacy when autologous transplant of a portion of the parathyroid is made in the forearm [13, 14]. Although all treatments proposed can help in preventing progressive calcification, the ability to restore ischemic tissue perfusion is questionable, which would explain the low rates of treatment success [14].

Vitamin K is recommended when calciphylaxis is associated with the intake of coumarin [9].

Sodium thiosulfate is gaining support as the agent of choice for calciphylaxis treatment [14]. It likely acts as a chelator by dissolving calcium salts and to inducing an antioxidant effect and, eventually, synthesis of endothelial nitric oxide levels, which improves blood flow and tissue oxygenation [9, 14]. It is well tolerated and considered a safe drug. Adverse effects, especially acidosis and bone resorption by osteoclasts and the activation of intravascular volume overload, are expected [14]. The dose commonly used to treat calciphylaxis is 25 mg administered intravenously three times a week, which can be used for many months to maintain the initial positive response [9, 14]. The biggest limitation is its common side effect, nausea [9].

The use of corticosteroids is controversial, although there is a case report that encourages its use [13].

Meticulous management of ulcers, the generous use of antibiotics, and prevention by debridement are measures universally accepted to increase the survival of these patients. There are studies supporting debridement as part of the treatment and additional use of hydrocolloid patches to guide healing [7, 9, 13, 14, 19]. The hyperbaric chamber has been reported as effective in aggressive debridement of ulcers with consequent greater healing by raising the partial pressure of oxygen in the affected tissues, which improves angiogenesis and phagocytosis, inhibiting bacterial growth and decreasing local tissue edema [7, 13]. The long-term benefit of this therapeutic modality should be validated in larger studies [13, 19].

Sepsis is the leading cause of death [13].

Nephrogenic Systemic Fibrosis

No specific treatment for NSF has universal approval. It seems that the improvement in renal function may be the most beneficial treatment and that transplantation could be the solution, although it does not guarantee symptomatic relief

[5, 7, 9, 14]. There are anecdotal reports of successful trials with thalidomide, pentoxifylline, high doses of intravenous Ig, prednisone, UVA phototherapy, cyclophosphamide, extracorporeal photopheresis, plasmapheresis, sodium thiosulfate, and topical calcipotriol under occlusion [9, 14, 19, 26]. Imatinib mesylate was recently reported to effect a significant improvement in three patients [14, 26]. Enrolling patients into physical treatment sessions such as deep tissue massages seem to be beneficial and do not involve additional risk [7, 14]. There also have been reports of spontaneous remission [19].

While gadolinium plays a major role in the development of NSF, exposure to this agent in patients who present with CRF does not always lead to this condition; it would therefore seem to be a multifactorial process [14].

Glossary

Dyschromia Alteration of the color of the skin.
Gynecomastia Enlargement of the breast in the males, caused by an excess of estrogens.
Macroglossia Excessively large tongue.
Microangiopathy Pathologic processes of the microvessels.
Pruritogenic substances Substances capable of causing pruritus (itching).
Raynaud's phenomenon Abrupt onset of digital paleness followed by cyanosis and erythema in response to cold.
Teratogenic effect Capacity of some substances of generate physical defects in the developing embryo.
Uroporphyrins Porphyrins produced by oxidation of uroporphyrinogen, which can be excreted in excess in the urine in the context of porphyrias.
Xerostomia Decreased salivary flow (dry mouth).

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Dermatologic Manifestations Among Transplant Recipients

45

Lídice Dufrechou and Alejandra Larre Borges

Key Points

- Organ transplant recipients undergo long-term immunosuppressant therapy that leads to reduced immunosurveillance as well as other adverse effects of these drugs
- The high rate of cutaneous complications in this population implies the need for interdisciplinary follow-up care teams with the participation of dermatologists
- Under immunosuppressive treatment, infections can be atypical and unusually disseminated
- Infections caused by rare pathogens must be considered in the differential diagnosis
- A high degree of suspicion and opportune agent isolation are essential
- Skin tumors, particularly squamous cell carcinoma, are of special relevance because of their more aggressive behavior, high risk of metastases, and lethality
- Advanced age at the time of the transplant is one of the most important clinical predictors of squamous cell carcinoma
- A larger ultraviolet radiation accumulation before the transplant also implies an increased risk
- Proactive prevention (i.e.: physical sun protection, use of sunscreens, individually adapted immunosuppressant medication) and the timely treatment of premalignant lesions can lower the risk of squamous cell carcinoma
- In a recent study, melanoma-specific mortality was elevated three-fold compared with nonrecipients, suggesting that melanoma behaves aggressively under transplant-related immunosuppression
- Patients who have had melanoma with lymph node invasion or metastatic disease are not candidates to receive a transplant

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Epidemiology

Solid organ transplantation constitutes a life-saving intervention for persons with end-stage organ disease. Transplants help increase the survival and quality of life of recipients, lowering treatment costs in most cases. According to the World Transplant Registry, 114,690 solid organ transplants were performed worldwide in 2013,

representing an increase of 1.8% over the previous year; kidney, liver, heart, and lung were the most frequently transplanted organs [1].

Long-term immunosuppression, which aims to downregulate the immune system in order to prevent allograft rejection, is necessary in recipients. New strategies in immunosuppressive therapy are associated with better patient and graft survival rates; however, adverse toxicities and long-term side effects associated with these agents present a number of challenges. Thus, current immunosuppression protocols are individualized and based on combined immunosuppressant therapies aiming to minimize administration of corticosteroids and to achieve a combined and synergic effect [2]. Such protocols vary according to the geographic area and the reference center. Immunosuppressants used with the purpose of maintaining the transplant are corticosteroids, calcineurin inhibitors (cyclosporine, tacrolimus, and tacrolimus MR), antimetabolites (mycophenolate mofetil, sodium mycophenolate, azathioprine), and mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus) [3, 4]. A variety of cutaneous complications and an increase in cutaneous malignancies, having a potentially great impact on patients' quality of life [8, 9], have been reported in this population, particularly among Caucasians [2, 5–7].

Overall, transplant complications can be divided into early and late, the former usually surgical and the latter medical. Infections are a common complication during the immediate postoperative and immediate perioperative periods, up to one month after the surgery. This risk persists as long as the transplant is maintained [10, 11]. Other frequent late complications are neoplasias, probably underreported, the risk of which is increased three to five times compared with in the general population [12].

Skin is a frequently affected organ in solid-organ recipients, affections are reported in 45–100% of patients; the frequency of dermatologic afflictions is 63% in our experience [2, 5]. This is also observed in the pediatric transplant population [13].

Skin Manifestations

Skin complications represent an important burden for transplant recipients for many reasons, such as their frequency, morbidity, and sizable impact on the quality of life of patients. Moreover, there has been increasing awareness of the public health implications of skin cancer in this population.

Most of the literature related to skin manifestations in solid-organ recipients comes from studies of renal and renal-pancreatic recipients. For practical matters we herein classify skin complications from solid organ transplants as infections, neoplasia, and adverse side effects of the immunosuppressant drugs. The aim of this chapter is to describe the most frequent dermatoses in solid-organ recipients regarding their epidemiology, clinical presentation, and therapeutic approach.

Discussion of the etiopathogenesis of the disorders is beyond the scope of this chapter. We focus solely on those etiopathogenic aspects that are distinctive in transplant recipients.

Infections

Skin infections are a relevant cause of death in solid-organ recipients, representing a growing diagnostic and therapeutic challenge [14, 15]. Their frequency varies between 27% and 66% according to different studies, the main causal agents being virus and fungi [2, 6–8, 16, 17]. The type of immunosuppressive drugs and their variable dosage in chronologic sequence after transplantation probably influence the type and appearance of skin infections [15]. The typical chronology of skin infections is wound infections, pyoderma, or the reactivation of herpes viruses in the first month after transplant, followed by opportunistic infections and reactivation of varicella zoster virus between months 2 and 5. After 6 months, as immunosuppression is reduced, the spectrum of causative organisms approaches that of the general population, with mycoses and human papillomavirus (HPV) infections dominating [15] (Fig. 45.1). Vulgar warts caused by different HPV serotypes and the infections caused by the herpesvirus family together with superficial mycoses such as tinea and pityriasis versicolor are the most frequently found in many studies [6–8, 13, 16, 17].

As mentioned, the frequency of these complications is directly proportional to the extent of immunosuppression and exposure to various potential
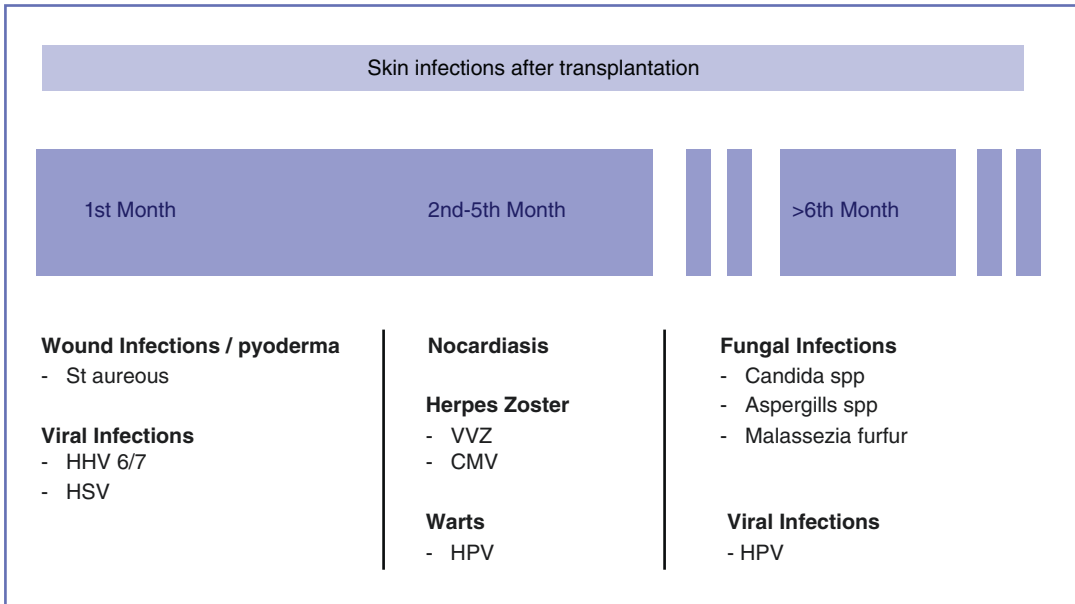
Fig. 45.1 Time frame of typical skin infections in organ transplant recipients. *HHV* human herpesvirus, *HSV* herpes simplex virus, *VZV* varicella zoster virus, *CMV* cytomegalovirus, *HPV* human papillomavirus

pathogens. Moreover, transplant recipients show complex interactions between chronic immunosuppression and the presence of risk factors such as deficient nutritional status, hyperglycemia, mucocutaneous barrier integrity loss, and subclinical activity of viral infections [18].

Viral Infections

Cytomegalovirus (CMV) is the most common viral infection following solid organ transplantation [19]. Not only does CMV directly cause morbidity and occasional mortality, but it also affects many short-term and long-term indirect factors that collectively contribute to reduced allograft and patient survival [20].

In light of the aforementioned, we detail cutaneous manifestations of CMV in solid organ recipients, although they are rare [21].

The main cutaneous viral infections among transplant recipients are caused by HPV, herpes simplex virus (HSV), and varicella zoster virus (VZV). The importance of viral infections lies in their morbidity and also in the fact that viral DNA has been found in squamous cell carcinomas (SCCs) as well as in Kaposi sarcoma (KS) of transplant recipients. [2, 22, 23].

Etiopathogenesis

CMV

It has been postulated that the dermis is relatively inhospitable to CMV; therefore, skin disease only occurs in a significantly immunocompromised host. As such, skin infection has generally been associated with disseminated disease, thus reflecting the overall degree of immunosuppression in these patients. The predominant defense against CMV is the major histocompatibility complex-restricted cytotoxic T cells, with growing evidence for the significant contributory role played by CD4+ T cells and humoral immunity. Immunosuppressive therapy suppresses cytotoxic cells in a dose-dependent manner and thus enhances viral replication once stimulated by other factors [24].

Pathogenically, in addition to direct viral effects, the CMV-induced immunomodulatory mechanism probably plays a role. The immunosuppressive effect of CMV may lead to an increased susceptibility toward opportunistic infection [15].

HPV

Since the advent of improved DNA technology, more than 100 distinct HPV subtypes have been

described with probably more to follow. HPV can be classified into two groups: cutaneous and mucosal subtypes. Cutaneous subtypes (cHPV) are predominantly found in cutaneous common and plane warts (mainly subtypes 2 and 4) and mucosal subtypes predominate in anogenital lesions such as condylomata acuminata [12, 22, 25]. Mucosal HPV subtypes can be divided into high-risk (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82) and low-risk (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108). Persistent infection with high-risk HPV (hrHPV), especially subtypes 16 and 18, has an essential role in the carcinogenesis of anogenital malignancies. Low-risk HPVs, especially 6 and 11, are responsible for about 90% of condylomata acuminata, which are not considered as precursor lesions of cervical cancer [12]. The HPV types detected in the renal transplant recipient (RTR) population are similar to those described in immunocompetent populations. However, the diversity of HPV types identified and the number of lesions increase in the RTR population [26].

HSV

HSV type 1 and type 2 (HSV-1, HSV-2) belong to the α-herpesvirus family. They are characterized by short replication cycles, rapid growth in culture, lysis of the host cell during replication, and latency in nerve root ganglia [23].

VZV

VZV also belongs to the α-herpesvirus family. Primary infection acquired through direct contact with skin lesions or by the respiratory route usually leads to chickenpox. After initial infection, VZV establishes latency in dorsal root ganglia and cranial nerves, and years or decades later it can reactivate as herpes zoster. The seroprevalence of VZV in adult recipients of solid organ recipients reaches 90%, while rates are lower in pediatric transplant patients. Solid organ transplant-seronegative adult recipients usually acquire infection through exposure in the community. Although very rare, VZV transmission by donor has been described [23]. Recipients with previous VZV disease or who have received vaccination have an increased risk

of herpes zoster. Other predisposing factors are advanced age, being a heart or lung recipient, and the use of mycophenolate mofetil [23].

Clinical Presentation

CMV

Skin infection by CMV has generally been associated with disseminated disease including hepatitis, pneumonitis, pancreatitis, kidney allograft dysfunction, colitis, and meningoencephalitis. As already mentioned, skin involvement is rare [21]. CMV usually presents as generalized maculopapular eruptions, but ulcers, nodules, vesicles, petechiae, and plaques may also be seen and can mimic other skin eruptions and cutaneous viral infections, especially herpetic infections. Cellulitis and ulceration, particularly involving the genital, perineum, and perianal areas, as well as necrosis of the mucosal membranes, can occur in more severe cases (Fig. 45.2)

Fig. 45.2 A 31-year-old woman. Renal transplant 2 months ago, taking tacrolimus, mycophenolate mofetil, and prednisone. Oral ulcer due to cytomegalovirus. The patient also presented malaise, asthenia, and weight loss

Fig. 45.3 A 52-year-old woman, renal transplant 37 months ago, taking cyclosporine A, mycophenolate mofetil, and prednisone. Recurrent viral warts in fingers

[15, 24]. CMV infection should be considered in a febrile immunosuppressed patient with skin involvement [21].

HPV

Recipients have a 15–50% chance of developing vulgar HPV warts within the first year post transplant, and 77–95% in the first 5 years [18]. These warts appear in multiple forms (hands, feet, and genitalia), predominantly on sun-exposed sites, and display a lesser tendency for spontaneous regression in comparison with the immunocompetent normal population [6, 15, 25] (Figs. 45.3 and 45.4).

HSV

HSV represents another cause of morbidity in these patients. An increased risk of developing HSV reactivations of up to 50% has been described with an incidence of up to 35% within the first 3 weeks following transplantation. In transplant patients HSV has an extensive presentation, together with necrosis, ulceration, prolonged evolution, and a higher risk of dissemination toward noble parenchyma such as the central nervous system, lungs, and liver (Fig. 45.5) [2, 8, 15, 27, 28]. Especially in heart and lung transplant recipients, severe esophagitis, bronchopneumonia, and encephalitis may occur [15]. Primo-infection during the post-transplant period is rare [29].

VZV

VZV is another pathogen that frequently affects transplant recipients [14]. Mustapić et al. (2011) carried out one of the largest trials regarding infection caused by VZV, in a total of 1139

recipients of kidney transplant between 1972 and 2010, showing a frequency of 3.51% and an average time of appearance of 2.13 years. Ninety-five percent of the studied patients presented with herpes zoster, while only 5% presented with chickenpox [30]. The risk of developing herpes zoster seems to increase according to age at the time of the transplant [28, 31]. In this population an increased risk of dissemination, postherpetic

Fig. 45.4 A 23-year-old woman, reno-pancreatic transplant 8 months ago, taking tacrolimus, mycophenolate mofetil, and prednisone. Multiple condylomata acuminata

neuralgia, and scars can be seen [28, 32] although in most cases the prognosis is favorable, with minimum morbidity and mortality [14] (Fig. 45.6).

Complementary Examinations

CMV detection using the polymerase chain reaction (PCR) is at present the most specific and sensitive method. The virus can be identified 1–2 weeks earlier than with cell culture or an antigen test [15].

Early skin biopsy is a useful and safe procedure for diagnosis confirmation. It shows cytoplasmic and nuclear inclusions and can be confirmed by immunohistochemistry in endothelial infected cells [33, 34].

Diagnosis of HPV warts, HSV, and VZS is often clinical. Conventional viral detection assays, including serologic assays and growth in cell culture, are not available for the diagnosis and tracking of HPV infection. Several types of HPV DNA tests are now available, including Southern blots, dot blots, in situ hybridization, PCR, and solution hybridization (hybrid capture assay). Of these, the PCR assay is the most sensitive [35].

Cervical Papanicolaou testing to detect and treat cervical intraepithelial neoplasia is one of the most important interventions that can be performed in transplant recipients concerning HPV infections and anal cancer screening [36].

HSV and VZV sometimes may require other diagnostic tools such as viral cultures, cytologic smear/Tzanck preparation of vesicular content, direct fluorescent antibody (DFA) studies, tissue biopsy, viral DNA detection by PCR, and serologic

Fig. 45.5 A 43-year-old man, renal transplant 44 months ago, bilateral herpes simplex

Fig. 45.6 Disseminated herpes zoster in a 46-year-old kidney transplant recipient taking tacrolimus, mycophenolate mofetil, and prednisone
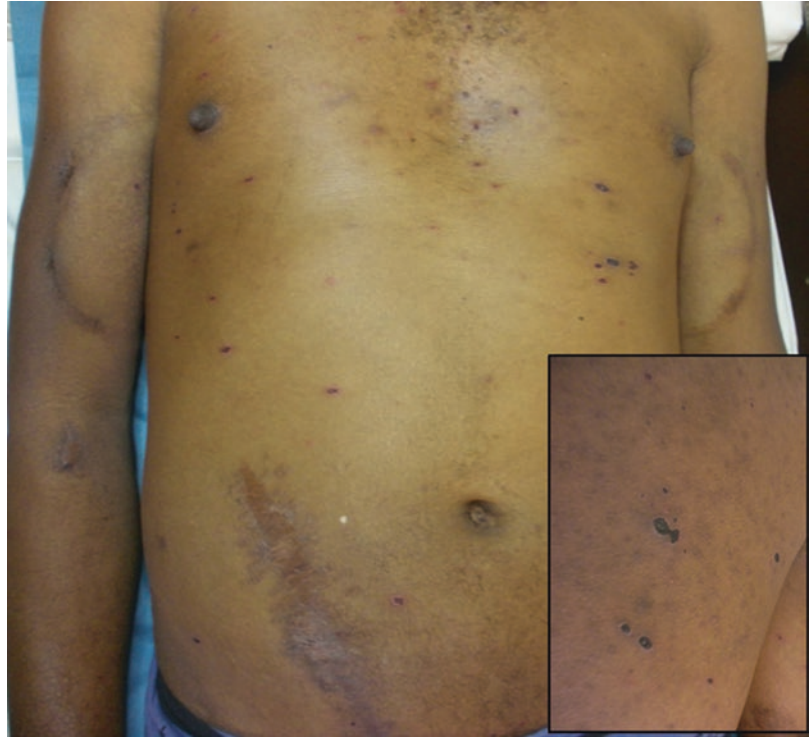
assays. The most rapid, inexpensive, and frequently used diagnostic tool is a cytologic smear (Tzanck smear) taken from the base of a freshly opened vesicle. The collected specimen is typically stained with Giemsa, Wright, or Papanicolaou stain and examined for virally induced cytopathologic features by light microscopy. Although the Tzanck test confirms HSV or VZV infection as the etiology, it cannot differentiate between them. These viral infections share similar cytopathologic features, necessitating immunohistochemical or DFA studies to type the specific virus [37].

Therapeutic Approach

CMV
An increased occurrence of late-onset CMV diseases attributable to prolonged antiviral prophylactic regimens has been seen in solid organ recipients [15].

Prevention of the infection in solid organ recipients includes universal prophylaxis or early

therapy considering individual risk factors for the development of CMV infection [38].

Regarding cutaneous manifestations caused by CMV there is no established guideline for treatment, so treatment strategies have been extrapolated from existing successful treatment of solid organ CMV infections and include intravenous ganciclovir and oral valganciclovir [34, 38]. Treatment of the mild or moderate disease consists of oral valganciclovir (900 mg/12 h). Intravenous ganciclovir is reserved for patients with severe disease or in situations where valganciclovir may be inadequately absorbed. The optimal duration of treatment is determined by the clinical and virologic evolution. Weekly determination of viral load or antigenemia should be performed to monitor response to treatment, which must be maintained until viral load decreases or antigenemia is negative. In any case, the minimum duration of treatment should not be less than 14 days [38].

HPV
Treatment strategy for HPV-associated cutaneous and external genital warts depends on the size,

location, and grade of the lesion. As cutaneous and external genital warts have very little malignant potential, cosmetics is frequently the main reason for treatment. In immunosuppressed patients, removal of warts may also be necessary because of the development of symptoms such as obstruction (in the case of anogenital warts), itching, and bleeding [36].

Treatment options are categorized as patient or clinician applied. There is no evidence that one modality is superior to the other, and the method chosen should reflect patient and provider preferences [36].

Regarding cutaneous warts, paring down of dead skin using a pumice stone, nail file, emery board, or scalpel is important to maximize the chance of cure. Soaking the affected skin for several minutes prior may help with paring. Products containing salicylic acid, cryotherapy, and imiquimod 5% cream represent the main treatment options. Salicylic acid comes in numerous preparations. It should be used in conjunction with an occlusive dressing such as duct tape that may increase the efficacy of the intervention. Treatment should ideally be continued for 1–2 weeks following the physical removal of the wart so as to minimize the chance of recurrence [36].

Cryotherapy can be performed using liquid nitrogen spray, a liquid nitrogen-soaked swab, or a cryoprobe cooled with nitrous oxide. It can be repeated every 3 weeks and should be a clinician-applied option [36]. Imiquimod 5% cream is a topical immune response modifier that induces cytokines locally without a direct antiviral effect. The usual regimen is to apply it once daily before bedtime, three times a week for up to 16 weeks [36].

For atypically appearing, recalcitrant, and recurrent cases, a biopsy is recommended given the high incidence of skin malignancies in transplant recipients [36].

Patient-applied therapeutic options for condylomata acuminata include imiquimod 5% cream and podofilox 0.5% solution or gel. The usual regimen for imiquimod 5% is to apply it once daily before bedtime, three times a week for up to 16 weeks. Podofilox 0.5% solution or gel arrests the cell cycle in metaphase, leading to cell death.

It should be applied twice daily for 3 days on, 4 days off, with a maximum of four cycles [36].

Dermatologist-applied therapies include cryotherapy, podophyllin resin 25%, and trichloroacetic acid (TCA) 80%. When performing cryotherapy, the freeze margin should extend 2–3 mm beyond the margin of the wart. Cryotherapy can be repeated every 3 weeks. Podophyllin resin 25% in tincture of benzoin is applied to the affected area, left to dry, and washed off after 6 h (maximum 0.5 mL per session). This process can be repeated after 1 week. TCA 80% can be applied to the affected tissue until it appears white or frosted. Multiple cycles of treatment are often needed [36]. Surgical options for the treatment of condyloma acuminata include infrared coagulation, laser surgery, and scissor excision.

The 2009 guidelines issued by the Infectious Diseases Community of Practice of the American Society of Transplantation recommend HPV vaccination before or after transplantation in eligible patients [39].

HSV

Since the cytomegalovirus prophylaxis era began (with drugs such as valganciclovir and ganciclovir), the incidence of HSV reactivation has lowered, nowadays having a 10% frequency [15].

Treatment of disseminated, visceral, or mucosal disease should be conducted with intravenous acyclovir doses of 5–10 mg/kg/8 h. In cases of severe illness the reduction of immunosuppression could also be considered. In limited skin disease, acyclovir, valacyclovir, or famciclovir can be used. In patients who do not respond to acyclovir treatment, resistance to the drug should be suspected, and foscarnet can be used as an alternative. Patients receiving prophylaxis against CMV during the post-transplant period do not require prophylaxis against HSV. When recurrence occurs after the end of treatment, suppressive therapy with antivirals should be considered until the level of immunosuppression can be lowered [37]. Brivudine can also be employed successfully, especially in the setting of renal insufficiency. Adequate clinical experience in organ transplant recipients has not yet been published [15].

VZV

Prevention against CMV used during the early post-transplant period can prevent reactivation of VZV, meaning that no additional prophylaxis is needed during this period. In those patients being evaluated for transplantation who are susceptible to VZV, attenuated Oka virus vaccine should be administered, which has been shown to be safe and effective in patients with advanced kidney disease. This vaccine should be administered at least 2–4 weeks prior to transplantation. Post-transplant vaccination is not recommended for VZV [37]. For children who are to undergo transplantation, prophylactic VZV immunization is strongly recommended [15].

Seronegative recipients who have presented significant exposure to VZV should receive post-exposure prophylaxis. The prophylaxis options for this include passive (VZV immunoglobulin within 96 h after possible exposure) and/or anti-viral immunoprophylaxis [15, 37].

Chickenpox treatment is intravenous acyclovir at doses of 10 mg/kg/8 h, which should be initiated as early as possible since earlier initiation leads to greater effectiveness. In cases of serious illness the use of intravenous immunoglobulin can be considered [37].

Herpes zoster can be treated on an outpatient basis with oral acyclovir, valacyclovir, or famciclovir. In cases of ophthalmic or otic involvement, intravenous acyclovir should be used [37]. Especially in patients with renal insufficiency, brivudine has been used successfully as it is metabolized in the liver before renal elimination [15].

Fungal Infections

Despite ongoing refinements in immunosuppressive agents, graft preservation, and surgical techniques, fungal infections remain a significant cause of morbidity and mortality in organ transplant recipients [40]. For practical matters, fungal infections will be classified as systemic, deep cutaneous fungal infections (DCFIs), and superficial.

Systemic fungal infections are associated with very high mortality in recipients [15, 40].

Probably for this reason, in the literature, there are more data on systemic fungal infections than in deep cutaneous and superficial fungal infections, which are mainly of interest to dermatologists.

Etiopathogenesis

Systemic and Deep Cutaneous Fungal Infections

Because of immunosuppression, transplant recipients have a significant risk of invasive fungal disease [41]. The main agents of systemic fungal infections are *Candida* spp., *Aspergillus* spp., and *Cryptococcus neoformans* [11, 15, 40, 41].

Candida species observed in transplant recipients include: *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. lusitaniae*, *C. rugusa*, *C. kefyr,* and *C. guilliermendii. C. albicans* ranks as the most common species with *C. glabrata* and *C. tropicalis* emerging as causative pathogens. *Candida* infections are generally derived from endogenous flora. Conditions that predispose to *Candida* colonization or overgrowth of the hepatobiliary, gastrointestinal, and genitourinary tract can facilitate fungemia and dissemination, especially with mucosal injury or bleeding and surgical manipulation. The frequency of non-*albicans Candida* isolates has increased. Proposed explanations include widespread use of fluconazole in the pre- and post-transplant period, prolonged pretransplant hospitalization and nosocomial acquisition, and the use of broad-spectrum antibiotics [40].

Concerning *Aspergillus*, species of medical importance include *A. fumigatus*, *A. flavus*, *A. niger*, *A. terreus*, *A. nidulans*, *A. glaucus*, *A. ustus*, *A. versicolor*, *A. oryzae*, *A. sydowi*, and *A. chevalieri. Aspergillus* infections may include one or more *Aspergillus* species from an individual patient. Lung and liver transplant recipients display the highest risk for invasive *Aspergillus* infection [40].

Aspergillus spores are ubiquitous and are frequently isolated from hospital ventilation systems, especially during periods of construction or renovation; community environmental exposures

may also occur. Inhalation of fungal spores is the primary mode of acquiring *Aspergillus*, and the lungs and upper respiratory tract are the most common sites of occurrence. Less commonly, *Aspergillus* from an infected or colonized open wound or surgical drain may pose a risk of airborne transmission to transplant patients housed in an intensive care unit [40].

DCFIs are caused by a variety of mostly tropical organisms, usually when they are implanted into the dermis or the subcutaneous tissue. They are most commonly attributed to traumatic inoculation of the fungi or foreign material containing the fungi into the skin such as thorns, splinters or other soil substrates, vegetation, or animals [42–44]. Agents implicated are *Blastomyces dermatitidis*, *Zygomycetes*, *Alternaria* spp., *Rhizopus* spp., *Fusarium* spp., *Acremonium* spp., and *Pseudoallescheria*, among others [42].

Superficial Fungal Infections

The principal agents involved in superficial fungal infections are *Malassezia* (*Malassezia* spp., *M. furfur*, *M. pachydermatis*) and dermatophytes. *M. furfur* is a dimorphic organism that resides on normal skin and within hair follicles. Dermatophytes include: *Microsporum* (*M. canis*, *M. audouinii*), *Trichophyton* (*T. mentagrophytes*, *T. rubrum*, *T. tonsurans*), and *Epidermophyton* (*E. floccosum*), which represent the etiologic pathogens of dermatophyte infections in recipients. Direct inoculations and traumatic abrasion are the usual routes of entry [40].

Several factors contribute to the high frequency of superficial fungal infections in these patients. This risk depends on factors such as diagnostic criteria, exposure to potentially pathogenic fungi, and geographic, socioeconomic, and hygienic conditions and time of immunosuppression [45]. The failure of cell-mediated immunity and the smaller amount of antigen-presenting Langerhans cells in the epidermis of these patients are essential for the development of infections [46]. Among drugs, corticosteroids in particular cause thickening of the corneal layer and prolong its removal, enabling fungal infections and their chronicity [45, 46].

Clinical Presentation

Systemic and Deep Cutaneous Fungal Infections

Solid organ transplant recipients have a significant risk of invasive fungal diseases (IFD) caused mainly by *Candida* spp. and *Aspergillus* spp., the former being the most frequent agent leading to morbidity and high mortality [11, 15, 41]. The incidence of invasive candidiasis has been estimated at approximately 2% in American adults and pediatric patients. The rate varies according to the organ transplanted: it is particularly high in abdominal solid organ transplants such as intestinal, pancreas, and liver transplantation while it is extremely uncommon after heart transplantation. Most cases of candidiasis occur during the first months after surgery [11, 41]. The main portal of entry is the gastrointestinal tract, followed by endovascular catheters and the urinary tract [41]. By contrast, primary cutaneous fungal infections occur several months after transplantation, have the tendency to progress slowly. and have a benign appearance that leads to a delay in diagnosis [47].

Systemic *Candida* infections can present serious diagnostic problems. In 10–13% of immunosuppressed patients, skin lesions as a result of hematogenous spread were diagnosed and ranged from subcutaneous nodules and pustules up to necrotic plaques [15]. However, the most common clinical forms are mucocutaneous, mainly oropharyngeal, esophageal candidiasis, vulvovaginitis, and wound infections [40, 48].

In general, DCFIs are associated with mortality rates from 4% to 10% in localized infections and can be as high as 83–94% in disseminated disease. Clinical presentation of DCFIs is variable and dependent on host-related factors, the type of fungal organism, and the mode of transmission. Skin lesions are nonspecific and may be misdiagnosed as cutaneous neoplasms or necrotizing lesions caused by coagulation disorders. Pathologic examination and skin tissue cultures are necessary for diagnostic confirmation. In this sense, clinical suspicion is essential [42]. According with González Santiago et al., most common clinical presentations of deep cutaneous fungal infections are encompassed or ulcerated nodules, plaques, ulcers,

erythematous macules, and evidence of tissue necrosis [42]. Individual reports exist of cutaneous aspergillosis due to direct inoculation or hematogenous spread. Skin manifestations are often unspecific and present, among others, as hemorrhagic bullae or erythematous plaques [15]. Rarely have cutaneous manifestations of other fungi such as *Cryptococcus neoformans*, *Exophiala jeanselmei*, *Wangiella dermatitidis*, or *Alternaria* species been reported [15].

Phaeohyphomycosis is a rare cutaneous or systemic infection caused by the dematiaceous family of pigmented fungi with several reports in solid organ recipients. Over 100 species have been isolated as etiologic agents, the most common being *Alternaria*, *Curvularia*, *Exserohilum*, and *Bipolaris*. The main route of transmission is traumatic inoculation by thorns, splinters or other soil substrates, vegetation, or animals [43]. Clinical presentation is variable: plaques, nodules, or ulcerative nodules and recurrent cellulitis, commonly in the lower extremities, as well as vegetative or infiltrative lesions. Systemic dissemination with multiple lesions and pulmonary infiltration has also been described [49, 50].

Disseminated histoplasmosis can involve skin and has been described exceptionally as soft-tissue masses and cellulitis [51, 52].

Superficial Fungal Infections

Superficial mycoses are frequently found in transplant recipients [6–8, 16, 17] and can predispose the appearance of deep mycosis [45]. They generally occur 6 months after transplantation[15].

Among the most frequent superficial fungal infections are pityriasis versicolor (*Malassezia* spp.) [8, 17, 29] according to some trials and dermatophytosis according to others [6, 7].

Among 102 organ transplant recipients examined, more than 35% had pityriasis versicolor, followed by mucocutaneous candidiasis (about 25%), onychomycosis (about 13%), and tinea pedis/*Candida* intertrigo (about 12%) [15, 53].

Clinical presentation of cutaneous superficial fungal infection seems to be similar to that in the nonimmunosuppressed host. Non-atypical, more severe, or widespread infections were observed in comparison with controls [5, 46].

Complementary Examinations

Systemic and Deep Cutaneous Fungal Infections

It is essential to develop diagnostic and therapeutic strategies to reduce the mortality attributed to the invasive fungal infections. It is substantial to achieve early accurate diagnosis and elucidate the necessity of establishing prophylactic protocols or not, depending on individual risk factors. To date, blood culture has been the reference procedure for the diagnosis of invasive candidiasis. However, its sensitivity for detecting *Candida* is only 50–75%, and the guidelines for diagnosis and management of *Candida* infections by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommend alternative techniques.

Two serologic diagnostic methods (the combined detection of mannan and antimannan antibodies and the quantification of the 1,3,β-D-glucan) are recommended in the ESCMID guidelines for candidemia detection in adults. PCR-based methods are useful when available [41]. When clinically suspected, an early skin biopsy including direct microscopy and culture of samples should be performed.

For DCFIs, routine histopathologic examination of lesional skin tissue remains the primary confirmatory method. It permits fast, presumptive identification of fungi and can also provide some insight into the diagnostic implication of some culture isolates. Because of the variable and longer turnaround time on tissue culture compared with routine histopathology, the latter is often relied on for the rapid diagnosis of DCFI. However, discrepancies between histopathology and culture results are sometimes seen [42].

Imaging procedures may help in the clinical approach; these include ultrasonography, computed tomography, and magnetic resonance imaging to highlight suspicious lesions for guided biopsies [54].

Superficial Fungal Infections

Although not essential, a laboratory diagnosis is helpful as the clinical diagnosis is not always

reliable. The key to diagnosis is the demonstration of the organisms in skin scales, hair, or nails. Scrapings are taken with a scalpel or nail clippers. They are commonly examined in potassium hydroxide and can be cultured on Sabouraud's medium. Skin scales, hair, and nails can be sent to a laboratory folded in a card (transport packs are available). Material from mucosal surfaces is better sent on a moistened swab [55].

Therapeutic Approach

Systemic and Deep Cutaneous Fungal Infections

There are no randomized studies of treatment for invasive or deep fungal infections among solid organ transplant recipients. Treatment should be based on the pathogen recovered as well as on the clinical syndrome and site of involvement, especially taking into account that if the site is accessible, and being possible, surgical removal of the focus is recommended [54].

The drug of choice for the treatment of candidemia is fluconazole (400 mg/day, preceded by initial dose of 800 mg/day). In cases of colonization by *C. glabrata*, prior treatment with azoles or the presence of severe sepsis or septic shock, the initial treatment of choice should be an echinocandin (caspofungin, anidulafungin, and micafungin), which have low toxicity and minor interactions with azoles [38].

Amphotericin B (AmB) deoxycholate has been regarded as the gold standard for therapy, but its administration is often associated with renal toxicity and infusion-related side effects. The lipid-associated amphotericin compounds, mainly the liposomal formulation, have the main advantage of decreasing nephrotoxicity, but there are no data that directly compare these agents with AmB for their efficacy to treat transplant population. The azole antifungal agents have a long-standing role in antifungal therapy. However, their interactions with the cytochrome P450 (CYP) enzyme system produces three- to five-fold increased levels of cyclosporine and

tacrolimus in most patients. New antifungal agents currently available require evaluation in solid organ transplant recipients. Drug interactions of a number of antifungal agents with immunosuppressants must be carefully considered when treating these recipients. The triazole agents are potent inhibitors of CYP34A isoenzymes with the potential to increase the levels of calcineurin inhibitors as well as sirolimus and everolimus. Duration of therapy must be individualized according to the fungal pathogen, the resolution of the process, and state of immunosuppression, and be guided by clinical, microbiological, or radiologic means [54].

Superficial Fungal Infections

Topical antifungals (e.g., terbinafine, imidazoles such as clotrimazole) are sufficient in most circumscribed infections including tinea corporis and pityriasis versicolor. The duration of treatment is 1–4 weeks. In the case of widespread lesions of pityriasis versicolor or in patients refractory to topical treatments (ketoconazole ointments and shampoo), oral antifungal therapy may be indicated; in particular fluconazole or itraconazole have been reported to be effective [56]. Nail infections, depending on the implied agent, require systemic treatment with terbinafine, 250 mg daily for 6–12 weeks or itraconazole, 400 mg daily for 1 week every month for at least 3 months [55].

Bacterial Infections

While bacterial extracutaneous infections are of great importance during the immediate posttransplant period [2], pyodermitis are reported with less frequency than the viral and fungal infections, and are mainly folliculitis and, exceptionally, anthrax [6–8, 17, 27].

Ethiopathogenesis

Generally, bacterial infections are the most common ones in tropical and subtropical countries [29].

In the first month after transplantation, perioperative and even nosocomial pathogens predominate. The frequent wound and urinary tract infections of this phase are increasingly being caused by antibiotic-resistant strains (vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus*, MRSA). In a study of 60 liver transplant recipients, 15% demonstrated MRSA on nasal swabs for the first time during inpatient treatment [15, 57].

Clinical Manifestations

Besides observing infections in wounds, the spectrum includes impetigo, folliculitis, abscess, cellulitis, and furuncles [29]. Since the residing bacterial flora is the same in transplant recipient patients as in the general population, causal agents of pyodermitis are the Group A streptococci and *Staphylococcus aureus* [29]. Furthermore, according to Ada et al., screening for nasal *S. aureus* carriage does not seem to assist in preventing staphylococcal bacterial infections in outpatient recipients [58]. The majority of subcutaneous abscesses are caused by staphylococci, and less frequently by Gram-negative bacteria or by a mixed flora. Case reports describe staphylococci following liver transplantation [15, 58].

Complementary Examinations

Isolation of the agent with an antibiogram is essential. Complementary examinations including imaging should be guided by clinical presentation and signs and symptoms of the infection.

Therapeutic Approach

Antibiotic therapy should be oriented on the results of the cultures and antibiogram. For staphylococcal infections, drugs of first choice are sulfonamides such as sulfadiazine and cotrimoxazole or, as an alternative in face of increasing resistance, imipenem/cilastatin combined with amikacin [15]. However, treatment should be individualized according to epidemiology and the bacterial resistance profile of the geographic area.

Other Infections

Numerous nontuberculous *Mycobacterium* (NTM) species can induce cutaneous lesions in solid organ transplant patients. Cutaneous lesions in this patient population characteristically begin as red to violaceous subcutaneous nodules that may be painful or only mildly symptomatic, and may progress to form abscesses or ulcers. Constitutional symptoms are typically absent. Nontuberculous *Mycobacterium* species associated with cutaneous lesions in solid organ transplant patients are *M. kansasii*, *M. marinum*, *M. haemophilum*, *M. fortuitum*, *M. crofulaceum*, *M. chelonae*, *M. avium*, *M. intracellulare*, and *M. abscessus* [59]. Isolation of the agent and directed therapy are essential.

Malignancies and Premalignancies

Skin cancers are more frequently seen in transplanted patients in comparison with the general population, and among them, nonmelanoma skin cancer is the most frequent [60, 61].

Squamous cell carcinomas (SCC) and basal cell carcinomas (BCC) represent over 90% of all the skin cancers in kidney transplant recipients [62].

The risk of developing BCC is proposed to be increased 10–16 times in comparison with the general population. Meanwhile, the risk of developing SCC is about 65–100 times higher in solid organ recipients [6, 60, 61].

Besides its prevalence, SCC in solid organ recipients present themselves more aggressively, with higher morbidity and mortality, and have a risk of metastasis ten times higher than in the general population [60, 63, 64].

Actinic Keratosis and Squamous Cell Carcinoma

Etiopathogenesis

Several risk factors for the development of SCC in transplant recipients can be identified besides those in common with the general population. Advanced age at the time of the transplant is one of the most important clinical predictors of SCC [65, 66]. A larger ultraviolet radiation accumulation before the transplant also implies an increased risk [64–67].

The preferential localization of SCC in photo-exposed areas supports the pathogenic role of ultraviolet radiation, as well as the fact that SCC occurs in areas with extensive actinic damage and epidermal dysplasia known as "field cancerization" [60]. Numerous recent studies that used PCR reported a high prevalence of HPV DNA in skin carcinomas of transplant patients [66]. In fact, immunocompromised patients have 50 times more risk of developing vulvar cancer and 100 times more risk of anal cancer compared with the general population [12]. E6/7 transcripts of HPV 8, 9, and 15 in actinic keratosis (AK) and SCC from these patients have also been found [60].

Having a history of SCC prior to the transplant seems to be one of the strongest predictors of subsequent SCC after transplantation [65, 66].

SCC develops more frequently in patients who have a low Fitzpatrick phototype, blue or light eyes, and male gender, the latter have also been found a factor that does not coincide in all the research studies [10, 64, 65, 68].

With regard to ethnic factors, we must point out the incidence in different populations that live in the same geographic area. In South Africa, SCC was reported only in Caucasian post-transplant patients [69]. The concurrence of factors such as low phototype and living in subtropical areas makes individuals under these conditions particularly susceptible to SCC, as also occurs in Australian non-native residents [64].

However, immunosuppression is the most critical and relevant aspect of transplant recipients in comparison with the general population, which can be explained by a reduction of the antitumor surveillance, suggesting that drugs may have an important role in carcinogenesis [70–73].

In addition, duration and level of immunosuppression are well-known risk factors [60].

Several trials suggest that patients who receive therapeutic regimes with three immunosuppressant drugs have more risk of developing skin cancer than patients who receive dual-drug therapy or sirolimus [60].

Azathioprine makes skin more photosensitive to ultraviolet A radiation. Skin DNA of patients with therapeutic doses of azathioprine contains 6-thioguanine, which is capable of accelerating the cutaneous carcinogenesis process [8, 10, 60, 72]. Moreover, maintained immunosuppression with azathioprine has been proved to increase the risk of developing subsequent SCC [74]. In turn, Cyclosporine has been shown to reduce reparation and apoptosis of keratinocytes after ultraviolet B radiation, leading to the accumulation of damaged DNA through inhibition of the mitochondrial permeability transition pore (MPTP) reparation system. The opening of this channel is induced in the presence of oxidative reduction, such as is caused by ultraviolet radiation that leads to cell death. However, in the presence of cyclosporine the damaged cells survive and are capable of initiating the carcinogenesis process [60, 73].

Clinical Presentation

AK is the initial lesion in a disease continuum that progresses to invasive SCC [75] and represents a serious problem in transplant recipients. Among 480 renal transplant recipients, AKs were detected in 54%. However, there have been no studies establishing its true prevalence [61, 62].

The most common clinical presentation of an AK is a red, scaling papule or plaque on a sun-exposed area. It is usually 1–3 mm in diameter, but can be several centimeters in size and numerous or confluent in sun-exposed areas. The surrounding areas may show evidence of sun damage. The scaliness can often be felt before it can be seen, so skin palpation is mandatory [75].

In transplant recipients the AKs clinically appear similarly as they do in the general population, and tend to "gather," which gives way to large areas of "field cancerization" (Fig. 45.7) [61].

The increase in *SCC* frequency among solid organ recipients is well known; its incidence varies

Fig. 45.7 A 66-year-old man, renal transplant 127 months ago, taking cyclosporine A, mycophenolate mofetil, and prednisone. Field of cancerization in the scalp with multiple actinic keratosis. The *arrow* points a basal cell carcinoma
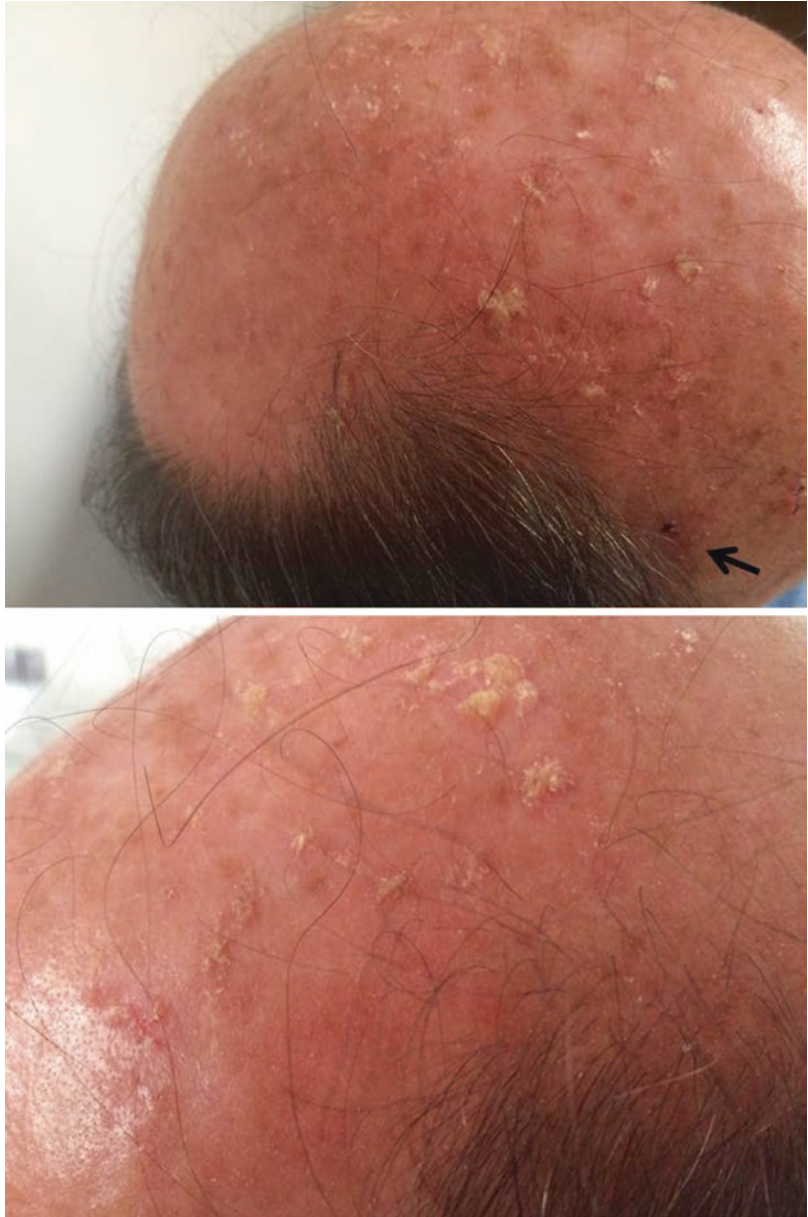
from 1% to 6.5% within the first 5 years after transplant, and from 6% to 35% in the following 10 years [67], reaching between 30% and 70% in kidney transplant recipients depending on the study population [65, 76]. The risk of developing subsequent tumors after the first one has been diagnosed has been less evaluated. A recent trial in New Zealand shows that out of 96 kidney transplant recipients with SCC, practically all developed multiple SCC [77]. Throughout the clinical course, 30% of patients presented a second tumor after the first year, 50% after the second year, 60% after the third year, and 80% after 5 years [77]. Furthermore, a Dutch review confirms this alarming increase in multiple tumor incidence. The authors found a cumulative incidence of a second SCC of 31% after 1 year, 62% after 3 years, and 75% after 5 years [63]. These percentages are clearly high if one takes into account that the cumulative risk of a subsequent SCC is 18% after 3 years in the general population [63, 77, 78].

SCC in solid organ recipients presents more aggressively, with higher morbidity and mortality, and has a risk of metastasis ten times higher than in the general population [60, 63, 64].

Clinically, SCC are characterized by scaling, erythematous skin plaques that initially can be confused with chronic inflammatory dermatitis. Lesions of SCCs are indurated as in immunocompetent patients, and have the characteristic of a slow-growing tumor that is painless, sometimes nodular. This tumor can grow very rapidly in organ transplant recipients, forming exophytic lesions that tend to ulcerate (Fig. 45.8). SCCs are often associated with signs of solar damage, notably elastosis, irregular pigmentation, telangiectasia, and leukokeratosis of the lower lip. However, transplant patients tend to be younger at the time of diagnosis if compared with immunocompetent individuals, and therefore have generally less sun damage [69]. The most common locations for developing SCC in transplant patients are sun-exposed sites, particularly the head and neck, followed by the upper extremity, trunk, and lower extremity. There is an increased incidence of lower trunk and upper extremity SCC compared with immunocompetent patients. The most common sites of SCC in the head and neck region are the scalp and the ear [69].

Contrary to what occurs in the general population where the incidence of BCC surpasses the incidence of SCC, in organ recipients the ratio BCC/SCC is reversed, so that SCC is more frequent than BCC in transplanted patients [10, 60, 67, 69, 79].

The specific mortality attributable to SCC varies between 1.5% and 15% according to different studies, the highest being from Australia. The authors ascribe this increase, among other factors, to the longer follow-up time [63]. Regarding this subject, the most effective measure proposed to decrease SCC morbidity and mortality is exeresis as soon as possible once the tumor is diagnosed [63] (Figs. 45.9 and 45.10).

Complementary Examinations

In general, AKs do not need complementary examinations. When suspected, in areas of field of cancerization, an early biopsy should be performed in order to exclude SCC [74].

Several imaging studies might be needed depending on the size and extension of the tumor. For deep tumors in high-risk areas, consider computed tomography/magnetic resonance imaging scans to evaluate deep extension or nodal involvement [74].

Therapeutic Approach

Treatment of AK and, therefore, the field cancerization is of vital importance, mainly if we take into account that while evolution of AK toward invasive carcinomas among nonimmunosup-

Fig. 45.8 A 78-year-old man, renal transplant 89 months ago, taking cyclosporine A, mycophenolate mofetil, and prednisone. Squamous cell carcinoma in the forearm

Fig. 45.9 A 35-year-old man, renal transplant 68 months ago, taking cyclosporine A, mycophenolate mofetil, and prednisone. Anal low-grade squamous cell carcinoma (Buschke–Lowenstein tumor)

Fig. 45.10 A 65-year-old man, renal transplant 185 months ago, taking cyclosporine A, mycophenolate mofetil, and prednisone. Left helix squamous cell carcinoma

pressed patients is 10%, among transplant recipients this percentage rises to 30% [73].

Among possible treatments of field cancerization, the most tested therapies are photodynamic therapy [59] and systemic retinoids. Patients treated with acitretin at 30 mg/day for 6 months presented a decreased incidence of SCC de novo [80]. Isolated AKs can be treated with classic medical or surgical methods such as cryotherapy. Managing transplant recipients with SCC is a challenge and requires a multidisciplinary approach. The lack of dermatologic control in recipient patients results in a low level of awareness of the problem and incorrect photoprotection, which results in an increased frequency of carcinoma. The appearance of this type of tumoral lesion is an indication for Mohs micrographic surgery if available, and a revision of immunosuppression [74, 81].

Ulrich et al. even proposed to biopsy the sentinel lymph node and to perform systemic therapy with retinoids in patients with clinically or histologically aggressive lesions [82].

Basal Cell Carcinoma

BCC is ten times more frequent in organ transplant recipients than in the general population [83].

Etiopathogenesis

A probable relationship between the occurrence of BCC and HLA DR I allele positivity was explored and confirmed in a Brazilian cohort of transplant recipients by de Carvalho et al. [84].

In addition, PTCH1 haplotypes containing certain alleles were shown to be associated with an increased BCC risk in an Italian population of organ transplant recipients. As in the case of SCC, more research to achieve early identification of individuals at high risk of developing cutaneous cancer after transplantation are needed. This would contribute to the adoption of targeted prevention strategies [83].

Clinical Presentation

In a series of retrospective cases where kidney transplant recipients with BCC were compared with controls, the BCC on the transplant recipients were observed to be more superficial, thinner, and pauci-inflammatory. Lesions were multifocal but without a tendency to metastasize or recur, and the average time for the development of such tumors was 10.5 years [85].

Clinical presentation seems to be similar to that in the general population, but specific studies about the clinical presentation are needed.

The cumulative incidence in renal transplant recipients for a second BCC is lower: 16% 1 year later, 37% after 3 years, and 51% after 5 years [62]. Around 50% of BCC are located on the head and neck, and in those cases where the BCC were multiple and subsequent they were located preferably on the trunk [63].

Complementary Examinations

A biopsy should be performed to confirm diagnosis. Since BBC has a low tendency to metastasize, imaging examinations are not necessary in most cases.

Therapeutic Approach

BCC developing under immunosuppression is generally no more aggressive than in immunocompetent persons, and should be treated surgically if possible [82].

Melanoma

Solid organ recipients have a two- to eight-fold increased risk of developing melanoma compared

with the general population, with an average time for its development of 5 years after transplantation [86–89]. However, these data are controversial, since other trials assert that the risk is similar to that for nonrecipient subjects [69].

Hollenbeak et al. published one of the largest trials related to this subject with a total of 89,786 kidney transplant patients between 1988 and 1998. These authors found an increased risk of developing melanoma of 3.6-fold [88].

Etiopathogenesis

Risk factors for melanoma in organ transplant recipients are similar to those in the general population: the presence of multiple nevi (also associated with immunosuppression) and fair complexion, family and personal history of melanoma, and exposure to ultraviolet radiation [90].

The immune system appears to play a role in melanocyte biology, and although the role of immunosuppression in melanoma requires additional study, several studies favor melanocyte proliferation. On a molecular level, a potential role for BRAF gene mutation in both benign nevi and melanoma in organ transplant recipients has been studied, and although preliminary evidence seems to suggest a lower frequency of BRAF mutations in organ transplant recipients, the role of immunosuppression in melanocyte biology remains of interest [60].

Clinical Presentation

There are no studies evaluating clinical characteristics of melanoma in transplant recipients.

The ABCD(E) mnemonic of melanoma has been a cornerstone of public health messaging for the community and physicians to help detect early melanomas. Following this rule, melanomas are characterized by A: *asymmetry*, B: irregular or poorly defined *border*, C: *color* variation from one area to another and different shades of tan, D: *diameter* greater than 6 mm, and E: *evolution* implying changes in size, color, or shape [91].

High-quality evidence suggests that dermoscopy (a noninvasive diagnostic technique for the in vivo observation of pigmented skin lesions performed with a dermoscope) is both more sensitive and more specific in classifying lesions as melanoma versus nonmelanoma than clinical examination with the naked eye alone [92]. Clinical and dermoscopic characteristics of melanoma are discussed in other chapters and are beyond the scope of this discussion.

Complementary Examinations

The earlier a melanoma is diagnosed and removed, the more likely is a cure for the patient. For this reason, if melanoma is suspected an early excisional biopsy should be performed. The remaining complementary examinations are essential for staging the tumor, and depend mainly on the clinical evaluation and the Breslow thickness in local stages.

Therapeutic Approach

Following a histologic diagnosis, the management of primary cutaneous melanoma is wide local excision with an appropriate clinical margin to minimize the risk of local recurrence and achieve histologic confirmation and accurate local staging while optimizing functional and cosmetic outcomes. The extent of the clinical resection is based on the Breslow thickness of the lesion [93].

In a recent study, melanoma-specific mortality in transplant recipients was elevated three-fold compared with nonrecipients, suggesting that melanoma behaves aggressively under transplant-related immunosuppression [90].

For transplant recipients who develop melanoma, physicians should perform an appropriate staging evaluation, including, if necessary, assessment of lymph node involvement and other distant spread. Along with surgery directed at the primary tumor, treatment should incorporate reduction or revision of immunosuppression, to the extent possible, to facilitate immunologic control of the tumor [90].

Regarding the opportunity for transplant in patients who have presented with melanoma, it is proposed that for patients with a history of melanoma in situ the transplant should not be delayed. In patients with a history of melanoma of Breslow thickness <1 mm and with a negative sentinel lymph node, a 2-year waiting period is

recommended in order to control recurrences or metastasis before the transplant. In patients with melanoma of Breslow thickness >2 mm it is advised to wait 5 years before the transplant because of the great risk of recurrence that exists and the uncertain behavior of melanoma against an immunosuppression background. Lastly, patients who have a melanoma with lymph node invasion or metastatic disease are not candidates to receive a transplant [61].

Concerning other malignancies, it is important to point out the larger incidence of KS in solid organ recipients. The risk of developing this neoplasia is thought to be up to 500 times larger in recipient patients than in the general population [2, 61, 93]. The association between human herpesvirus 8 (HHV-8) and KS is evident in transplant patients, although doubt remains over whether this tumor is produced by reactivation of the virus, as a consequence of immunosuppression, or due to a primary infection transmitted by the transplanted organ [94, 95]. The fact that this virus has a larger prevalence in certain geographic areas such as the Mediterranean and Africa implies a larger frequency of KS in recipients coming from these regions. In fact, seven cases of KS were observed in 175 kidney transplant recipients in central and southern Italy, in a 10-year follow-up, with a 14.8% seropositivity for HHV-8 in that population [94].

Contrary to these results, in a total of 3815 solid organ transplants performed over 26 years, only five patients with KS were identified, representing 0.1%, in a central European population where the HHV-8 prevalence is lower [93].

Approximately 23% of seropositive patients at the time of the transplant will develop KS during the following 3 post-transplant years on a standard immunosuppressant regime [96].

KS tends to be more aggressive in kidney transplant recipients. The risk of visceral compromise is related to the transplanted organ and/ or the degree of immunosuppression, representing between 25% and 30% among kidney transplant recipients [61].

Since the course of KS depends on the level of immunosuppression, the treatment cornerstone is to taper down immunosuppressive regimens to the lowest possible level associated with lesion regression. Specific local or, less frequently, systemic treatment modalities can be used, such as chemotherapy. Recently, mTOR inhibitors have proved effective in the treatment of KS among kidney recipients. Despite these favorable results, more research on this topic is necessary [97, 98].

Side Effects of Immunosuppressant Drugs

The side effects of immunosuppressant drugs (SEID) comprise dermatoses highly frequent in kidney transplant recipients, and it is estimated that those related to the Cushing syndrome are present in 55–90% of the recipients [17], the latter being specifically related to worse quality of life [7].

Most studies agree that SEID occur more frequently during the first post-transplant stage, and are therefore related to a high immunosuppression charge and tend to reduce as time passes [17, 27].

The most frequently mentioned SEID are acneiform reactions, gingival hyperplasia, striae, skin hyperpigmentation, hirsutism, purpura, and ecchymosis [7, 8, 17, 27].

Glossary

Antibiogram A record of the susceptibility of specific pathogenic bacteria to antibiotics. Antibiograms are often taken into account to define a rational selection of an antimicrobial therapy.

Antimetabolites Drugs that interfere with one or more enzymes or their reactions that are necessary for DNA synthesis. They affect DNA synthesis by acting as a substitute for the actual metabolites that would be used in the normal metabolism.

Calcineurin inhibitors Suppress the immune system by preventing interleukin-2 (IL-2) production in T cells.

Cryotherapy Treatment using low temperature for the removal of some skin lesions by freezing them. The most common product used by doctors is liquid nitrogen.

Mohs micrographic surgery
Microscopically controlled surgery used to treat common types of skin cancer. During the surgery, after each removal of tissue and while the patient waits, the tissue is examined for cancer cells. This examination informs the decision for additional tissue removal. Mohs surgery is one of the many methods of obtaining complete margin control during removal of a skin cancer.

mTOR inhibitors   mTOR inhibitors are a class of drugs that inhibit the mTOR, which is a serine/threonine-specific protein kinase belonging to the family of phosphatidylinositol 3-kinase (PI3K)-related kinases (PIKKs). mTOR regulates cellular metabolism, growth, and proliferation.

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Further Information Can Be Found at the Following Internet Addresses

Committee for the Care of Immunosuppressed Patients of the Dermatologic Oncology Working Group: www.ado-homepage.de.

German Transplantation Society (Deutsche Transplantationsgesellschaft e.V., DTG): www.d-t-g-online.de.

German network of dermatologists in private practice specializing in the care of organ-transplant recipients (the ONKODERM e.V. network): www.onkoderm.de.

German Dialysis and Renal Transplantation Board (Kuratorium für Dialyse und Nierentransplantation e.V., KfH): www.kfh-dialyse.de/kfh/index.html.

German Association of Organ-Transplant Recipients (Bundesverband der Organtransplantierten e.V., BDO): www.bdo-ev.de.

German Working Group for Nursing Care in Transplantation (Arbeitskreis AKTX-Pflege e.V.): www.aktxpflege.de.

Skin Care in Organ Transplant Patients Network, Europe: www.SCOPEnetwork.org.

Paraneoplasias

46

Fernanda Razera and Renan Rangel Bonamigo

Key Points

- Paraneoplastic diseases are not directly related to the invasion of the primary tumor or its metastases
- Dermatologic lesions are the second most common form of paraneoplastic syndrome
- They may be the first manifestation of the neoplasia, enabling an earlier diagnosis of the tumor; and may improve the prognosis and help monitor its recurrence
- There is a wide variety of clinical presentation of paraneoplastic dermatoses
- It is important to know the dermatoses with possible association with malignant neoplastic diseases and to conduct appropriate clinical investigation of the patient

Introduction

Cutaneous manifestations of malignant neoplastic diseases may be classified as metastatic lesions of the skin, genodermatoses associated with neoplasias, dermatoses induced by environmental carcinogens, and paraneoplastic dermatoses [1].

Paraneoplastic diseases are hormonal, neurologic, or hematologic disorders and clinical or biochemical alterations associated with malignant neoplasias that are not, however, directly related to the invasion of the primary tumor or its metastases [2, 3]. Dermatologic lesions are the second most common form of paraneoplastic syndrome, the first being endocrine manifestations [3].

The mechanisms involved in the onset of dermatologic lesions have not yet been recognized for most manifestations. The production or depletion of biologically active mediators such as growth factors, cytokines, or hormones is believed to be involved in the pathogenesis of cutaneous findings [4]. Another possibility is that an immune response induced by the tumor causes skin changes [1].

Although paraneoplastic dermatoses are rare, they are very important in the practice of dermatology because they may be the first manifestation of the neoplasia. Hence, recognizing them enables an earlier diagnosis of the tumor. It may also improve the prognosis and help to monitor its recurrence [1, 4].

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In 1976, Helen O. Curth [5] defined six criteria that establish the causal relationship between dermatoses and neoplasia, characterizing the paraneoplastic dermatoses (Box 46.1).

> **Box 46.1 Curth's Postulates**
> 1. Dermatosis and neoplasia begin almost concurrently
> 2. Both conditions present a parallel course
> 3. The condition is not recognized as part of a genetic syndrome
> 4. A specific tumor occurs with a given dermatosis
> 5. Dermatosis is not common
> 6. There is a high percentage of association recognized in the literature

Skin Manifestations

In addition to the clinical presentation, each paraneoplastic dermatosis is discussed regarding its probable etiopathogenesis, complementary examinations for the diagnosis, and the therapeutic approach. All figures in this chapter are provided by the Dermatology Service of UFCSPA (Brazil).

Malignant Acanthosis Nigricans

Approximately 80% of cases of acanthosis nigricans are benign and associated with obesity and presentations of insulin resistance. In this situation, onset is usually at an early age. However, patients with abrupt onset and more extensive or severe manifestations in adulthood, above 40 years of age, must be investigated for neoplasias [1, 3].

Malignant acanthosis nigricans (MAN) is clinically characterized by hyperkeratosis, hyperpigmentation, and velvety papillomatosis in body folds (axillae, inguinal region, cervical region, popliteal and cubital fossae) (Figs. 46.1 and 46.2). The lesions can progress to a verru-

Fig. 46.1 Acanthosis nigricans located in the cervical region

Fig. 46.2 Acanthosis nigricans located in the axilla

cous and thicker appearance. The oral mucosa may be involved, and this presentation is usual in cases of MAN. The palmoplantar regions may also be involved. There may be a complaint of pruritus [1, 4].

The histopathologic findings are in the epidermis and show that it is a proliferative disorder. The main findings are hyperkeratosis, papillomatosis, acanthosis with elongation of the dermal projections, and thickening of the stratum spinosum [1].

The likely mechanism involved in the development of MAN is the production of transforming growth factor α (TGF-α) by the tumor cells that stimulate the proliferation of keratinocytes by the epidermal growth factor [6]. Other growth factors, such as insulin-like growth factor 1,

fibroblast growth factor, and α-melanocyte stimulating hormone, may also be involved [7].

There may be an association with other paraneoplastic dermatoses, also with characteristics of dermal proliferation, such as the sign of Leser-Trélat (SLT) and tripe palms, suggesting that these dermatoses share the same pathogenesis [8–11]. This association should increase the suspicion of the presence of neoplasia.

The malignant neoplasias most commonly associated with MAN are adenocarcinomas, especially gastric (73%). Other tumors reported are pulmonary, esophageal, liver, and ovary [11]. The onset of the lesions may occur before, concomitantly with, or after the diagnosis of neoplasias. In a recent series of cases, 22% of lesions preceded the diagnosis of neoplasia and in 57% of the cases they were concomitant [11].

The treatment of the neoplasia generally resolves the skin lesions. The course of MAN is correlated with tumor behavior [1]. The prognosis is poor, and mean survival time is 2 years after the acanthosis is diagnosed [7, 10].

Acquired Pachydermatoglyphy or "Tripe Palms"

This condition is also called palmar acanthosis, palmar acanthosis nigricans, palmar hyperkeratosis, and palmar keratoderma. It presents as palmar thickening with marked palmar ridges and grooves, which exaggerate the dermatoglyph (digital print), giving it a rough, velvety appearance (Figs. 46.3 and 46.4). This clinical aspect recalls the villosities of the intestinal mucosa, thus earning the term tripe palm [3, 12]. There is no predilection for sex, and it occurs more often in elderly patients.

Acanthosis and hyperkeratosis are predominantly observed on histopathology; other findings reported are papillomatosis, dermal mucinosis, and increased mastocytes [1, 13].

As in MAN, there seems to be participation of growth factors and stimulation of epidermal receptors of these factors. High serum levels of TGF-α have already been identified in patients with pachydermatoglyphy [14].

Fig. 46.3 Palmar thickening with marked palmar ridges and grooves, which exaggerate the dermatoglyphs

Fig. 46.4 Palmar thickening with marked palmar ridges and grooves, which exaggerate the dermatoglyphs

This dermatosis shares a few epidemiologic, morphologic, and histologic factors with MAN and is present in association with it in 75% of cases [1, 4, 13]. Hence, some authors believe that it may be a palmar manifestation of MAN [1].

About 90% of the cases of dermatoglyphy are associated with malignant neoplasias [1, 13]. The neoplasia most associated is pulmonary, followed by gastric tumors. When there is an association with MAN, the most prevalent neoplasia is gastric [13].

In approximately 60% of cases, the diagnosis of acquired dermatoglyphy occurs before or concomitant with the diagnosis of the tumor [13]. The skin lesions usually run parallel to the course of the neoplasia.

Sign of Leser-Trélat

The SLT presents as a sudden increase in the quantity and rapid growth in the size of seborrheic keratoses. The keratoses are characterized as verrucous papules, with various diameters and colors, located on the trunk, limbs, axillae, neck, and face [3, 4, 15] (Figs. 46.5 and 46.6). There may be inflammatory signs and pruritus. It may be associated with other paraneoplastic manifestations, especially MAN, which increases suspicion regarding the presence of the neoplasia [3].

The SLT primarily affects individuals over 60 years old, without a predilection for sex or race [3].

Its association with malignant neoplasms is still controversial. The age group with the greatest number of seborrheic keratoses is also the one with the most tumors, which makes it difficult to establish a cause–effect relationship [3, 4]. However, it is important to distinguish it from multiple seborrheic keratoses that appear throughout life and whose onset begins in the second or third decade of life [15].

Fig. 46.5 Verrucous papules, with various diameters and colors, located on the trunk

Fig. 46.6 Verrucous papules, with various diameters and colors, located on the trunk

There are reports of cases of an increase in number and size of seborrheic keratoses that are not associated with the onset of neoplasias, even after long periods of observation [16, 17]. Other case–control studies, comparing the number and aspect of seborrheic keratoses in patients with a diagnosis of cancer and paired controls, found that only two patients with tumors presented with SLT as described in the literature, showing that it is a rarer process, which makes it difficult to study [18]. In the other patients studied there was no difference in the number and location of lesions [18].

However, there are hundreds of reports in the literature describing the onset of SLT in many different neoplasias. Most of the tumors are adenocarcinomas, especially in the gastrointestinal tract. There are reports of lymphoproliferative diseases, as well as carcinomas, for instance of the breast, bladder, prostate, kidneys, lungs, ovaries, and melanoma [3, 15].

Skin lesions generally run parallel to the course of the tumor. The neoplasias associated with the SLT are aggressive and may result in an expectation of less than 12 months in most cases [15]. Despite controversy, patients with the SLT must be investigated for the presence of neoplasias by taking a medical history and performing a complete physical examination, biochemical tests, chest X- ray, mammogram, cytopathologic test of the cervix, prostate-specific antigen, endoscopy, and colonoscopy [15].

Acquired Ichthyosis

The clinical aspect of acquired ichthyosis is similar to that of dominant autosomal ichthyosis. However, acquired ichthyosis begins in adulthood, different from the hereditary form which usually begins before the age of 13 years [1]. It is characterized by diffuse, small, white or brownish scales with a rhomboid aspect and high margins. The scales predominate on the trunk and extensor surface of the limbs (Fig. 46.7) [1]. There is no palmoplantar and fold involvement [4].

The histopathologic examination reveals orthokeratosis, a thinner or absent granular layer, and mild acanthosis. There is no dermal inflammation or it is minimal [4].

The great majority of cases of acquired ichthyosis associated with described neoplasias is associated with Hodgkin's lymphoma (70%), but there are reports of an association with non-Hodgkin lymphoma, multiple myeloma, leukemia and, less frequently, solid tumors [4].
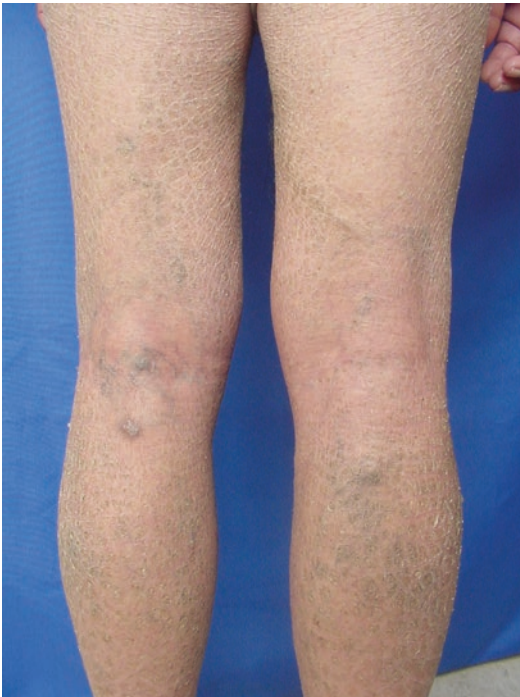
Generally the acquired form in adults is associated with various non-neoplastic diseases, such as malnutrition, hypothyroidism, and sarcoidosis, Hansen's disease, the use of medications, and acquired immunodeficiencies, such as human immunodeficiency virus infection, graft-versus-host disease, and disorders post bone marrow transplantation [3].

The pathophysiology involved in the development of acquired ichthyosis is not yet known. Some authors believe that there is malabsorption of vitamin A [19]. Others have published evidence that in patients with Hodgkin's disease there is less synthesis of dermal lipids [20].

Acquired ichthyosis is usually diagnosed weeks or months after the neoplasia is discovered; it is rarely the initial symptom of neoplasia [1, 21]. The course of ichthyosis usually runs parallel to that of the neoplasia. Moreover, ichthyosis can occur in association with other dermatoses such as dermatomyositis (DM), erythema gyratum repens (EGR), and Bazex syndrome [3].

Bazex Syndrome

Also called paraneoplastic acrokeratosis, this condition is associated with malignant neoplasias in the vast majority of cases reported in the literature. It is characterized by erythematous to violaceous colored papulosquamous plaques, located in acral areas such as the nose, auricular pavilion, hands, and feet, besides ungual alterations [1, 22]. The lesions are distributed symmetrically. There may be pruritus [1].

The syndrome is described in three stages: in the first, erythema and psoriasiform scaling is seen on fingers, hands, feet, and margin of the helix, as well as violaceous erythema and pityriasiform scaling on the nasal dorsum. Alterations of the nails often occur, and include fragile nails, subungual hyperkeratosis, and onycholysis (Figs. 46.8 and 46.9). In the second stage the scaling completely covers hands and feet, producing a violaceous keratoderma. The skin becomes edematous and the palms may take on a honeycomb aspect. The scaling may affect the entire auricular

Fig. 46.7 Small, white/brownish scales with a rhomboid aspect and high margins in the extensor surface of the legs

Fig. 46.8 Erythema and psoriasiform scaling on the dorsum of fingers associated with alterations of the nails

Fig. 46.9 Erythema and psoriasiform scaling on the dorsum of fingers associated with alterations of the nails

pavilion. At this stage the first localized or systemic symptoms of the neoplasia may occur. In the third stage there may be involvement of additional areas, such as knees, arms, and scalp [23].

It predominates in male patients and the age of onset is usually around 60 years [22].

The histologic examination of the papulosquamous lesions shows hyperkeratosis, parakeratosis, acanthosis, dyskeratotic keratinocytes, and a perivascular mononuclear infiltrate [22].

The neoplasias most commonly associated with the Bazex syndrome are squamous cell carcinomas of the head and neck or squamous cell tumors of unknown origin, which present metastases to the cervical lymph nodes [22]. The most frequently described tumors are those of the oro-

pharynx, larynx, esophagus, and lungs. These findings suggest that mechanisms involved in the development of this syndrome are specific to tumors in these locations [22].

In more than 60% of the cases, the onset of skin lesions occurs on average 11 months before the symptoms or tumor diagnosis, and they are one of the earliest signs of neoplasm [22, 24].

The differential diagnosis must be made with psoriasis, eczema resistant to treatment, and superficial fungal infections. In psoriasis generally the entire auricular pavilion is involved and usually affects the palmoplantar area, not the dorsum of the limbs. Furthermore, the involvement of the helix and the bulbous enlargement of the distal phalanx are characteristic of the Bazex syndrome. The Bazex syndrome must always be ruled out in acral dermatoses that do not respond to appropriate treatment [24].

When Bazex syndrome is suspected, the evaluation should begin with a detailed history and physical examination. Initial examinations include complete otorhinolaryngologic evaluation, chest X-ray, complete hemogram, erythrocyte sedimentation rate, biochemistry, iron, tumor markers, and a search for occult blood in the stool. If the otorhinolaryngologic evaluation and chest X-ray are inconclusive, an upper gastrointestinal endoscopy can be indicated. If there is anemia or occult blood in the stool, a colonoscopy is appropriate. Based on findings of the history and physical examination, it may be necessary to perform a computed tomography (CT) evaluation of the chest, abdomen, and pelvis. If the initial evaluation is negative, the patient must be reassessed every 3 months [24].

The lesions are resistant to a variety of topical treatments, but they improve significantly in response to treatment of the neoplasia. Despite the improvement of the skin lesions, the ungual lesions usually do not present a regression [22].

Erythema Gyratum Repens

EGR is a rare and clinically specific panneoplastic syndrome associated with a malignant

neoplasia in 82% of the cases reported [25]. It is considered mandatory to perform an investigation for neoplasia in patients who have been diagnosed with this syndrome [3, 26].

It is more common in males (2:1) and the mean age of onset of symptoms is 63 years. It predominates in Caucasian patients [26].

EGR is characterized by the presence of polycyclic, serpiginous erythema with scaling on its border and is rapidly progressive (1 cm/day), producing ring-shaped erythematous, concentric figures similar to a wood surface. It is generally located on the trunk and proximal extremities and spares hands, feet, and face. There is usually pruritus [3].

The histologic examination is usually nonspecific with mild to moderate hyperkeratosis, epidermal spongiosis, and perivascular lymphocytic infiltrate [1].

The tumors most commonly associated with EGR are of the lung, esophagus, breast, cervix, and stomach [3, 26, 27]. EGR lesions precede the diagnosis of the neoplasia in 80% of the cases by 4–9 months [3, 4, 26, 27].

The pathophysiology of EGR is still unknown. It is believed that immune mechanisms are involved, since immunosuppression may accompany the resolution of the skin condition [4]. Although it is not a consistent finding, there is evidence of granular deposition of immunoglobulin G (IgG) and protein C3 in the basal membrane of affected areas [28]. Some authors believe that the keratinized cells present proteins that share epitopes with the tumor and its proteins, which would explain a cross-reaction [28].

EGR has already been described in pregnancy and in the presence of non-neoplastic diseases such as tuberculosis, CREST syndrome, and Sjögren syndrome [4].

The lesions usually are completely resolved when the neoplasia is treated and the course of the dermatosis is usually parallel to the course of the neoplasia. In patients with metastatic lesions, the EGR lesions usually persist or recur [4, 27, 28]. The use of antihistamines and topical corticosteroids is not very effective [4].

Necrolytic Migratory Erythema

Necrolytic migratory erythema (NME) is the cutaneous manifestation of the glucagonoma syndrome. This syndrome is characterized by the presence of NME, loss of weight, diabetes mellitus, cheilitis, stomatitis, diarrhea, and anemia [3, 12, 29]. Skin lesions are considered the most specific component of the glucagonoma syndrome and are the first manifestation of the syndrome in 67% of cases, but 100% of the patients with glucagonoma will develop NME lesions at some time during the course of the disease. When the tumor is diagnosed early, there is reasonable potential to cure the neoplasia [29–31].

NME usually appears in the fifth or sixth decade of life, but there are reports of patients aged 19–84 years. There is no predominant gender. The glucagonoma syndrome is an extremely rare disorder with an estimated incidence of 1 in 20 million persons per year, but may be higher. The rate of malignant neoplasia in glucagonoma syndrome is 57–100%. The 5-year survival rate is less than 50% [1, 29–31].

It presents clinically as maculopapular, annular, or arciform erythematous lesions that increase centrifugally, developing blisters that lead to necrosis and erosion. The lesions are confluent and present a crusted periphery. The center of the lesions usually heals with hyperpigmentation, but may take on a lichenified or psoriasiform appearance in intertriginous areas [30]. They predominate in the lower extremities, trunk, face, and inguinal region. The lesions are usually more marked in the perioral and perianal region. Thus, the clinical presentation is similar to that of other dermatoses associated with zinc deficiency and other nutritional deficiencies [4, 12].

Besides the cutaneous findings, the patients present systemic symptoms such as weight loss, glucose intolerance, anemia, thromboembolic disease, hypoaminoacidemia, and psychiatric disorders [1, 3].

Increased glucagon appears responsible for most of the clinical symptoms. However, the deficiency of fatty acids, amino acids, and zinc

also contributes to the pathogenesis of skin lesions [4, 30]. The catabolic state produced by the excess of glucagon appears to be responsible for the nutrient depletion [3, 30].

The histologic findings vary according to the phase of evolution of the biopsied lesion. In general the anatomopathologic examination can be characterized by psoriasiform hyperplasia with confluent parakeratosis, epidermal vacuolization, and necrosis with the formation of subcorneal pustules [1, 12].

When associated with tumors, NME is the result of α cell pancreatic tumor [1]. NME is also seen in association with other pancreatic diseases, malabsorption syndromes, liver failure, inflammatory bowel disease, chronic pancreatitis, and celiac disease without the presence of glucagonoma [4, 29]. These conditions are called pseudoglucagonoma syndrome.

The differential diagnosis of NME includes dermatoses such as enteropathic dermatitis, pellagra, psoriasis, seborrheic dermatitis, and pemphigus [29].

Because it is rare the diagnosis is usually late, and therefore it has a worse prognosis. Most of the patients already present metastases at the time of diagnosis and a consequent shorter survival, since the only means of cure is tumor surgery [29].

The treatment of symptoms with the administration of somatostatin/octreotide or chemotherapy is also effective. The effect expected from these treatments is the normalization of glucagon levels, which makes the lesions disappear [32]. In cases of liver metastasis it might be effective to embolize the hepatic artery [30].

Dermatomyositis

DM is a severe inflammatory myopathy associated with cutaneous findings whose cause is unknown. DM has been divided into two groups: (1) idiopathic (not associated with neoplasia) and (2) paraneoplastic (associated with neoplasia) [1]. The clinical findings do not differ between the two groups [3]. The cutaneous findings may occur in the absence of myositis, known as amyopathic DM. Patients with DM appear to have a greater frequency of malignant neoplasia than the general population. Some studies demonstrate a three-fold greater incidence of neoplasia in patients with DM [33]. However, patients with polymyositis appear not to present this association [33, 34].

Patients with DM associated with malignant neoplasia are between the age of 50 and 60 years, a larger age group than that of the patients with the idiopathic form of DM [34]. There is controversy regarding the predilection for sex; in patients without neoplasia DM predominates in women, while DM associated with neoplasia appears to be more frequent among males [1, 33, 34].

The most typical cutaneous lesions in DM are Gottron's papules (erythematous-violaceous papules or plaques, with discrete scaling, located in metacarpophalangeal and interphalangeal joints; Fig. 46.10) and heliotrope (erythematous-violaceous lesions, with or without edema, symmetric, located in the periorbital region). Other cutaneous findings of DM are malar erythema, poikiloderma in photoexposed areas, periungual telangiectasia, cuticular hypertrophy, and cicatricial alopecia. Myositis is characterized primarily by proximal muscular weakness [35].

The anatomopathologic examination that is characteristic of paraneoplastic DM is dermatitis with a vacuolar interface, with irregular lymphocytic inflammation and variable deposition of mucin [1].

Fig. 46.10 Gottron's papules

Skin lesions generally begin before the diagnosis of neoplasia, and most of the tumors are diagnosed 1 year after the diagnosis of DM [34]. The neoplasias most often associated with DM are ovaries, lung, pancreas, stomach, colorectum, and lymphomas [33].

The factors associated with neoplasia in patients with a diagnosis of DM are the presence of constitutional symptoms, the rapid onset of DM or polymyositis symptoms, the absence of Raynaud's phenomenon, and high levels of erythrocyte sedimentation and creatine phosphokinase [36]. Other factors that also appear to increase the risk of neoplasia in patients with DM are old age, male gender, presence of skin necrosis and dysphagia, while the presence of arthritis and interstitial lung disease appear to be less prevalent in paraneoplastic DM [37].

In patients with DM a careful clinical evaluation, routine laboratory tests, a chest, abdominal, and pelvic CT scan, upper gastrointestinal endoscopy, a mammogram, and a gynecologic assessment should be performed [33, 36]. The risk of a diagnosis of cancer is not diminished even 5 years after DM is diagnosed, indicating the need to remain vigilant for the detection of neoplasia [33]. The 5-year survival rate in patients with DM and neoplasia was reported to be 10% and in patients with idiopathic DM 74% [34].

The treatment of paraneoplastic DM is not different from that for idiopathic disease, and prednisone, azathioprine, and methotrexate can be used, besides topical medication, sunscreen, and hydroxychloroquine [35]. The surgical treatment of the neoplasia appears not to change patients' survival but does diminish progression to myositis [33]. In patients with a prior history of neoplasia and clinical worsening of the DM lesions, it is necessary to investigate the possibility of tumor recurrence [36].

Paraneoplastic Pemphigus

Paraneoplastic pemphigus (PNP) is an autoimmune bullous disease with polymorphic mucocutaneous lesions, associated with benign and malignant lymphoproliferative processes [1, 38].

PNP is associated with a series of autoantibodies that can affect multiple organs such as the kidneys, the smooth and striated muscle system, small bowel, colon, and thyroid. According to some authors PNP is only one of the manifestations of this syndrome, and they therefore propose the term paraneoplastic autoimmune multiorgan syndrome. This term is not yet widely accepted in the literature [39, 40].

In PNP there is no predilection for gender. It may occur at any age from 7 to 80 years, but the mean time of onset is usually around the age of 55 [38].

The typical initial manifestation is progressive and painful stomatitis, which may extend to the pharynx, larynx, esophagus, eyes, nose, and genitals. The oral lesions are located preferentially on the lateral border of the tongue and extend to the vermillion of the lips. It is believed that the pain in stomatitis occurs because of the location of the ulcerated lesions. There are lesions in the palmoplantar region [1, 41, 42].

The cutaneous findings are polymorphic and can occur in a same individual. They can be classified as [40]:

- Pemphigus: superficial, flaccid vesicles and blisters, erosions and crusts, occasionally with some erythema
- Bullous pemphigoid: erythematous papules associated or not with tense blisters
- Multiform erythema: polymorphic lesions, mainly erythematous papules and erosions/ulcers
- Graft versus host: erythematous-squamous papules
- Lichen planus: violaceous, squamous papules, flat, with intense involvement of the mucosae

PNP is the only form of pemphigus that involves tissues not covered only by stratified squamous epithelium. Approximately 40% of the patients develop pulmonary involvement [42]. Bronchiolitis obliterans with progressive ventilatory insufficiency is the main cause of death in PNP [38].

In the histologic examination of PNP, suprabasilar acantholysis, vacuolar degeneration of the interface with necrosis of keratinocytes, and

lichenoid inflammatory infiltrate can be observed. The clinical variants present a correlation with the finding of the anatomopathologic examination. This variation represents the different pathogenetic mechanisms involved in the PNP: it may be a disease mediated by B cells, such as pemphigus, or by T cells, as in lichen planus [1, 38, 40]. Direct immunofluorescence shows intercellular deposits of IgG and C3 in the epidermis and/or linearly at the dermoepidermal junction. Indirect immunofluorescence in rat bladders identifies the IgG antibody reaction with simple columnar and transitional epithelium, different from other bullous diseases [1, 4, 38].

The serum autoantibodies are identified by immunoblot analyses of patients' serum samples on human epidermal extracts. The serum autoantibodies identified in PNP are antidesmoglein 1 and 3, as well as members of the family of epithelial proteins plakin (desmoplakin I and II, envoplakin, periplakin), bullous pemphigoid antigen 1 (BPAg1), plectin, and α2-type macroglobulin 1 protein 1 [42] (Table 46.1).

The origin of the disease is not yet clear, but it is believed that the immune response in PNP can originate in two ways: (1) immune response to neoplastic antigens with antibodies that have a cross-reaction to the epithelial antigens or (2) pathogenic autoantibodies synthesized by the tumors that deregulate the immune system by cytokine synthesis [42].

The diagnostic criteria for PNP are shown in Table 46.2:

In two-thirds of the patients with PNP, the neoplasia is diagnosed before the skin lesions. The most commonly associated neoplasias are non-Hodgkin lymphoma, chronic lymphocytic leukemia, and Castleman's disease in children [42]. It has already been described, less frequently, in association with solid tumors such as thymomas and sarcomas [41].

The evaluation of patients with suspected PNP should include a complete physical examination, skin biopsy for histopathology, direct and indirect immunofluorescence, and immunoprecipitation. Evaluation for the presence of neoplasia should include a complete blood count, proteinogram, and a CT scan of the chest, abdomen, and pelvis, besides biopsies directed at lymph nodes, bone marrow, or solid tumors when indicated [45].

The clinical aspects of the disease may mimic those seen in eruptions secondary to drugs, erythema multiforme, Stevens–Johnson syndrome, or toxic epidermal necrolysis [42].

Table 46.1 Paraneoplastic pemphigus: autoantigens in pathogenesis [43]

Antigen	Molecular weight (kDa)	Location
Desmoglein 3	130	Desmosome: extracellular
Desmoglein 1	160	Desmosome: extracellular
Envoplakin	210	Desmosome: intracellular
Periplakin	190	Desmosome: intracellular
Bullous pemphigoid antigen 1	230	Hemidesmosome/lamina lucida
Desmoplakin I	250	Desmosome: intracellular
Desmoplakin II	210	Desmosome: intracellular
Plectin	400	Hemidesmosome: intracellular

Table 46.2 Paraneoplastic pemphigus: diagnostic criteria [44]

1. Clinical	Painful mucosal erosion(s) with a polymorphous skin eruption culminating in vesicles and/or bullae in the context of an occult/confirmed neoplasm
2. Histopathology	Intraepidermal acantholysis, vacuolar interfacial dermatoses, and keratinocyte necrosis
3. Immunofluorescence (direct)	Deposition of complement and IgG in intercellular epidermal spaces and in the epidermal basement zone in linear granular lesions
4. Autoantibodies	Detection in the serum similar to that seen in pemphigus
5. Immune complexes	Characteristic complex of four proteins immunoprecipitated from keratinocytes with serum autoantibodies

The autoimmune disease is difficult to treat and does not improve even when the neoplasia is treated effectively. For autoimmune treatment corticosteroids, immunosuppressive drugs (cyclosporine, cyclophosphamide), plasmapheresis, immunoglobulin, and rituximab may be used [38]. The prognosis for PNP is not favorable; mortality can reach 90% of cases. Most of the patients die of pulmonary complications (bronchiolitis obliterans and pneumonias), infections, or complications resulting from the neoplasia itself [38, 42]. Patents with erythema multiforme-type lesions and the presence of keratinocyte necrosis, especially if associated with extensive lesions at presentation, may have a worse prognosis, with a faster and more severe outcome [44, 46].

Sweet Syndrome

Also called acute febrile neutrophilic dermatosis, Sweet syndrome (SS) is characterized by four cardinal aspects: fever, peripheral leukocytosis, painful erythematous plaques on limbs, face, and neck, and dense neutrophilic infiltrate in the dermis. SS has been described in association with different neoplasias, autoimmune diseases, and infections, especially respiratory [47]. Currently it is classified as classic (idiopathic), associated with neoplasias or drug induced [48].

It is believed that 20% of the cases of SS are associated with neoplasias [47, 49, 50]. When associated with neoplasias there is no predilection for the female gender as in idiopathic SS. The median age of the patients with SS and neoplasia is 52 years [1]. Patients with paraneoplastic SS appear to be on average older than patients with the idiopathic and drug-associated subtypes [51].

The lesions usually appear abruptly and evolve within days or weeks. SS is characterized by well-demarcated erythematous-purpuric, painful plaques, with an irregular surface, and because of severe dermal edema they may have the appearance of pseudovesicles. The lesions have annular arrangements and asymmetric distribution, generally on the upper extremities, neck, and face (Figs. 46.11 and 46.12) [1, 47].

Different from the idiopathic form, in the lesions associated with neoplasias there is no history of infection of the upper airways; neutrophilia also may be absent, and the skin lesions are usually more severe and may involve the mucosae [47, 49, 50]. Other common differences in paraneoplastic SS are immature cells in the differential of the blood count, presence of anemia, and thrombocytopenia or thrombocytosis [50]. Anemia and abnormal platelet count appear to be the most readily identified difference between the two groups [47]. Proteinuria is commonly found when there is renal involvement. Therefore the possibility of neoplasia must be considered in all patients with a diagnosis of SS, older age, more severe skin manifestations, and an abnormal differential of leukocytes and/or cytopenias [50,

Fig. 46.11 Well-demarcated erythematous-purpuric plaques, irregular surface, annular arrangements, and asymmetric distribution, on the upper trunk

Fig. 46.12 Appearance of pseudovesicles

51]. The characteristics of paraneoplastic SS are described in Box 46.2.

Box 46.2 Characteristics of the Paraneoplastic Sweet Syndrome
- A history of upper airway infection or other associated conditions is unusual
- No predominant gender
- More severe skin lesions
- Skin lesions precede the diagnosis of neoplasia in most cases
- Extracutaneous involvement in >50% of the patients
- Absence of neutrophilia in >50% of the patients
- Frequent presence of anemia and abnormal platelet count
- High rate of recurrence generally associated with tumor "relapse"

There may be the presence of hemorrhagic blisters and ulceration, rendering the SS lesions similar to the lesions of atypical gangrenous pyoderma. This led some authors to suggest that it is the same disease with different spectra [47].

There may be symptoms of involvement of other systems in SS. When associated with neoplasias, 50% of the patients will present extracutaneous involvement particularly of the musculoskeletal, renal, and ophthalmic systems, and less commonly of lungs and liver [50].

A dense neutrophilic infiltrate is found in the histopathologic examination, filling the middle and upper dermis. Epidermal alterations are rare. A few patients with SS associated with hematologic neoplasia present leukemia cutis associated with neutrophilia [4, 52]. Histologic aspects of vasculitis are absent, but often endothelial edema and karyorrhexis (nuclear fragmentation of neutrophils) are found [49].

The physiopathogenesis of SS is still unknown. In SS associated with neoplasia, the most accepted pathogenesis mechanism is increased production or inappropriate regulation of inflammatory cytokines such as interleukin (IL)-1, IL-3,

IL-6, IL-8, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor [48].

The tumors most frequently associated with SS (85% of the cases) are the hematologic neoplasias, especially acute myeloid leukemia, lymphoma, myelodysplastic syndrome, and chronic myeloid leukemia. Outstanding among the solid tumors (15% of cases) are those of the genitourinary tract, breast, and gastrointestinal tract [1, 49, 50]. In two-thirds of the patients with paraneoplastic SS, dermatosis is the initial sign either of recurrence/persistence of the tumor or of asymptomatic metastasis [49, 50]. The suggested initial evaluation of patients with suspected paraneoplastic SS is described in Box 46.3.

Box 46.3 Initial Evaluation of the Presence of Neoplasias in Patients with Sweet Syndrome [49]
- Detailed clinical history
- Complete physical examination
  - Evaluation of lymph nodes, thyroid, oral cavity, skin
  - Digital rectal examination
  - Gynecologic evaluation in women
  - Urologic evaluation in men (testicular and prostatic)
- Laboratory evaluation
  - Complete blood count
  - Carcinoembryonic antigen
  - Biochemical
  - Qualitative urinalysis
  - Investigation of occult blood in stool
- Complementary examinations
  - Chest X-ray
  - Endometrial evaluation in menopausal patients, or patients with a history of uterine bleeding, obesity, infertility or hormone treatment
  - Colonoscopy in patients older than 50 years

Patients with a diagnosis of SS should initially be evaluated for hematologic neoplasia and solid tumors. The hemogram should be repeated every 6–12 months in patients with a diagnosis of SS,

since the diagnosis of hematologic neoplasia may be late [49]. A complete blood count must be performed in all patients with a diagnosis of hematologic neoplasia who develop new or recurring SS lesions. It is more unlikely that solid tumors will develop after 12 months' follow-up of these patients, thus there is no indication for an exhaustive investigation. Likewise, the onset of new SS lesions in patients with diagnoses of solid tumors needs evaluation for recurrent or persistent neoplasia [49].

The cutaneous signs and symptoms of SS present a rapid resolution after the administration of corticosteroids, independent of the course of the neoplasia [1, 50].

Pyoderma Gangrenosum

Pyoderma gangrenosum (PG) is an uncommon ulcerative disease whose pathogenesis is still not clear. It is generally associated with other inflammatory diseases such as intestinal inflammatory disease, rheumatoid arthritis, monoclonal gammopathy, systemic lupus erythematosus, and others [53]. Two clinical forms are described [53]:

- Typical form: characterized by painful nodules or pustules that form necrotic ulcers with undermined violaceous borders. It is located preferentially on the abdomen, buttocks, lower extremities and face. Generally associated with intestinal inflammatory disease
- Atypical form; characterized by hemorrhagic blisters and rapidly growing more superficial lesions. Common in the upper extremities, generally associated with hematologic diseases or neoplasias (Fig 46.13)

The age at onset of the lesions is adults on average 45 years old for the typical form and 52 years for the atypical form [53].

The histopathologic findings are not specific, but help rule out other causes of ulcerations and confirm the aspect compatible with PG, and moreover the findings usually vary with the evolution of the lesion and the biopsy site [1, 53]. Earlier PG lesions show a dense neutrophilic

Fig. 46.13 Pyoderma gangrenosum: necrotic ulcers with undermined violaceous borders

infiltrate in the dermis, with a few neutrophils extending to the epidermis. Vasculitis is absent [1, 53, 54].

The clinical and histologic similarity between the hemorrhagic SS and the atypical PG leads some authors to believe that it is the same disease with a different spectrum. The name neutrophilic dermatosis attributable to myeloproliferative diseases has already been suggested [47, 54].

The association of PG with neoplasia is described as 7% [54]. The most common are hematologic neoplasias, especially acute myeloid leukemia [54]. Multiple myeloma is the second neoplasia most frequently described in association with PG [1]. There are reports of an association with solid tumors, but these are rarer, and outstanding among them are colon, prostate, bladder, breast, adrenal glands, and lung [54].

The presence of the bullous variant of PG suggests the need for a careful investigation of the patients for hematologic neoplasias, including bone marrow biopsy. The onset of PG in patients with relatively benign hematologic diseases, such as myelodysplasia and polycythemia rubra vera may indicate the more aggressive progression of the disease, including a malignant transformation, indicating the need for a meticulous evaluation of these patients. In patients with acute myeloid leukemia, the onset of PG indicates a worse prognosis [54].

The treatment of PG is lengthy and based on the use of corticosteroids and immunosuppressors. The lesions of atypical PG usually heal

faster than those of the typical PG [53, 54]. The course of PG in association with neoplastic diseases has not yet been well established [1].

Multicentric Reticulohistiocytosis

Multicentric reticulohistiocytosis (MR) is a rare systemic histiocytic disease that preferentially affects skin and synovium. In 40% of the cases the initial symptom is in the joint, and in 30% of cases the initial symptoms are cutaneous [55]. It is a progressive, insidious, and self-limiting disease that disappears within 7 years after onset [1].

The great majority of the cases occur in Caucasian patients, with a slight predominance in females (1.85:1). It may occur at any age, but the mean age of patients at the onset of the symptoms is 50 years [55].

It is characterized by the presence of papules or nodules up to 2 cm in diameter, of pinkish, brownish, or grayish color. Preferential location is the hands, followed by the face, arms, trunk, legs, auricular pavilion, and cervical region [55]. The pathognomonic lesions are the "coral beads," which are papules found along the nail bed. Other characteristic findings are palpebral xanthelasma and vermicular lesions on the nostril rims [4, 55].

Multicentric reticulohistiocytosis is associated with symmetric destructive arthropathy which occurs in any joint, most frequently hands and knees, but it may also affect other joints. The radiologic examination shows well-circumscribed punched erosions and reabsorption of the juxta-articular zone with disproportionate changes compared with the clinical examination [1, 55].

There may be systemic symptoms such as dysphagia, loss of weight, pruritus, weakness, lymphadenopathy, and others [55].

The anatomopathologic examination shows nonencapsulated, well-circumscribed nodular infiltrate of histiocytes and multinucleated giant cells with a "ground-glass" type eosinophilic cytoplasm [1].

In immunohistochemistry the cells are positive for CD68 and CD45, showing that it is an infiltrate originating in monocytes and macro-phages, and it has a variable expression of T-lymphocyte markers (CD3), nonreactivity for B-cell markers (CD10–CD22), Langerhans cells, and dermal dendrocytes (S100 and factor XIIIa) [55, 56].

In laboratory tests there may also be increased erythrocyte sedimentation velocity, anemia, and hypercholesterolemia.

The association of MR with neoplasia varies from 20% to 30% in the literature [55, 56]. There is no predominance of a specific type of tumor associated with MR. MR has already been described in association with cancer of the breast, uterus, ovaries, pleural mesothelioma, lymphomas, melanoma, penis, gastric tract, pancreas, and lung [55, 56]. The clinical course of MR is not predictable or parallel to that of the neoplasia [1, 55]. Although MR does not present all criteria for a paraneoplastic dermatosis, this association appears important. This justifies its investigation for this diagnosis [55].

The use of antiproliferative drugs may alter the course of MR, and outstanding among them are cyclophosphamide, methotrexate, azathioprine, and chlorambucil [55].

Necrobiotic Xanthogranuloma

Necrobiotic xanthogranuloma (NX) is characterized by the presence of plaques and firm, yellowish nodules, which often occur in the periorbital region [57]. NX was distinguished from normo- and hyperlipemic plane periorbital xanthomas by Kossard and Winkelmann in 1980 [58].

The mean age at lesion onset is 52–56 years, but it may appear from the ages of 20 to 80. There is no predilection for gender [59, 60].

NX is characterized by the onset of well-demarcated yellowish-orange plaques (xanthomatosis) or firm subcutaneous nodules, located mainly on the face, more specifically the upper and lower eyelids. Most of the patients also present with lesions on the trunk and extremities [4, 57]. The size may vary from 0.3 to 25 cm in diameter [1]. It may be associated with ulceration, telangiectasias, erythematous-violaceous margins, and atrophy. There may be pruritus [57].

NX is a systemic disease. The most affected extracutaneous sites are the respiratory tract (epiglottis, larynx, pharynx, bronchi, and lungs) and heart [57].

Histopathologically, the epidermis and upper dermis are generally normal. The histopathologic findings extend from the middle dermis to the subcutaneous tissue. Granulomatous inflammation consisting of spumous histiocytes, lymphocytes, foreign body type multinucleated giant cells, and Touton giant cells alternated with foci of collagen necrobiosis is observed [1, 57]. In these necrobiosis foci cholesterol clefts are observed. This characteristic can help distinguish necrobiosis lipoidica from NX [1, 4, 57].

The most frequently found alterations in the laboratory tests in XN patients are leukopenia, C4 deficiency, increased erythrocyte sedimentation velocity and, in the electrophoresis of serum proteins, monoclonal gammopathy of the IgG-κ IgG-λ type [57]. Because of this gammopathy, many patients are submitted to a bone marrow biopsy for investigation. The most often reported findings are plasmocytosis or abnormal plasmocytes, multiple myeloma, and myeloproliferative disease [57].

The association of NX with hematologic disorders has already been clearly established. Benign monoclonal gammopathy is present in the great majority of cases [57, 59–61]. Malignant hematologic diseases associated with NX are multiple myeloma, chronic lymphocytic leukemia, Hodgkin's disease, and non-Hodgkin lymphoma [57, 59–61]. Hematologic alterations may appear before or after the beginning of the skin lesions (8 years before to 11 years after the beginning of the skin lesions) [61]. Hence, patients with NX must be followed for a long time to rule out the development of hematologic diseases [59, 61].

The treatment is usually unsatisfactory, with high rates of recurrence in the options already described. There is a report of the use of alkylating agents (chlorambucil, cyclophosphamide, melphalan), corticosteroids (topical, systemic, and intralesional), laser (CO_2, Nd:YAG), methotrexate, azathioprine, systemic antibiotics, and surgical excision of the lesions [57]. NX is a

chronic and progressive process characterized by the onset of new lesions and by the gradual evolution of the oldest lesions [60]. The treatment of the lymphoproliferative disease does not always result in remission of the cutaneous symptoms [57].

Acquired Hypertrichosis Lanuginosa

Acquired hypertrichosis lanuginosa (AHL) is a rare condition with a sudden, late onset, no family history, and strong association with the presence of malignant neoplasias [62].

It occurs predominantly in female patients, and the age of onset of the symptoms usually varies from 40 to 70 years with a mean of 54 years [62, 63].

It is characterized by the development of soft, velvety, nonpigmented hairs, often on the face. It may appear in other regions such as the trunk, axillae, and limbs, but it spares the palmoplantar regions and genitals, since it does not follow a specific distribution according to gender [1, 63]. The progression of the appearance of hairs is craniocaudal. Associated symptoms are glossitis and hypertrophy of the papillae of the tongue. It may be associated with other paraneoplastic manifestations, such as acanthosis nigricans and seborrheic keratoses [1, 63].

In histopathology, the follicle of the lanugo-type hairs is observed, which extend almost parallel to the epidermis surface, different from the normally almost vertical position of the follicles. Besides, many follicles are of the "mantle hair type." The mantle appears to be formed by two buttons or epithelial chords that extend around the follicle, creating a kind of apron at the site where the sebaceous duct would normally be found [62, 64].

The pathogenesis of AHL has not yet been completely elucidated. It is believed that products secreted by the tumors, such as cytokines or growth factors, may stimulate tumor growth, besides promoting the proliferation of other cells such as those of the pilous follicles [63].

In women the neoplasia most associated with AHL is colorectal carcinoma, followed by lung

and breast cancer. In men, lung cancer is the most often found neoplasia, followed by colorectal carcinoma [63]. Therefore, patients with AHL without a diagnosis of neoplasia should undergo biochemical tests, chest X ray, colonoscopy, and gynecologic evaluation (in women) [63].

Hair growth may occur 2.5 years before the tumor is diagnosed up to 5 years after the diagnosis. In general, patients with AHL already present advanced metastatic disease at the time of diagnosis; consequently, the prognosis is poor [63].

Successful antitumor therapy is associated with regression of the hairs [63] (Table 46.3).

Pruritus

Paraneoplastic pruritus (PP) is a frequent manifestation in hematologic neoplasias, and may affect 15–50% of the patients with polycythemia vera and lymphomas, but it is quite rare in other forms of neoplasia [65].

PP may be defined as a systemic reaction to the presence of the tumor or of the hematologic neoplasia not produced by the presence of tumor cells or by tumor treatment. PP may precede the diagnosis of a tumor and may also disappear when the tumor is treated. Tumor recurrence leads to the reappearance of the lesions, and the evolution of the tumor disease may also be associated with an increased intensity of the pruritus [65].

The prevalence of pruritus in the population with malignant neoplasias is still unknown. In one study it was demonstrated that generalized pruritus without any other cutaneous manifestation presents a prevalence of 5.9% if we take into account all patients with neoplasias (41/700) evaluated in the study, or 12.97% if we only consider the patients with neoplasias and cutaneous symptoms (41/316) [66].

PP generally appears in skin without any lesions or with lesions secondary to scratching, such as excoriations, nodules, prurigo, lichenification, hyper- or hypopigmentation, and scars [65, 67]. Another clinical form of PP is aquagenic pruritus, characterized by the onset of pruritus within minutes of contact with water at any temperature, without other cutaneous lesions. In more than 30% of the patients, aquagenic pruritus is associated with polycythemia vera or other lymphoproliferative diseases [65, 67]. Pruritus in Hodgkin's disease often begins in the legs and is more severe at night, but soon becomes generalized [68]. Patients with Hodgkin's disease may present a recent onset of eczematous lesions [67].

It has been recognized that the prevalence of pruritus depends on the type of neoplasia [65]. Pruritus is more prevalent in hematologic neoplasias such as Hodgkin's disease, non-Hodgkin lymphoma, leukemia, lymphomas, polycythemia vera, and multiple myeloma [65, 67]. It may occur less frequently in solid tumors such as breast, lung, and gastrointestinal cancer [4, 65, 67].

The type of evaluation to which patients with chronic pruritus of undetermined causes should be submitted is still under discussion. A large 5-year population cohort study with 8,744 patients demonstrated that patients with chronic pruritus had a higher incidence of hematologic (relative risk (RR) 2.02, 95% confidence interval (CI) 1.48–2.75) and bile duct (cholangiocarcinoma) (RR 3.73, 95% CI 1.55–8.97) neoplasias [69]. Despite these relative risks, the incidence of these neoplasias per person per year is extremely low: 0.0003 for cholangiocarcinoma and 0.0016 for malignant neoplasias. Hence, the evaluation for neoplasia in patients with chronic pruritus without skin lesions should be limited to those with signs and symptoms suggesting the presence of a tumor, after clinical evaluation (history and physical examination, with attention to the lymph nodes), initial laboratory tests (complete blood count, lactate dehydrogenase, and liver function) [67, 69]. The initial evaluation will determine the need to complement the evaluation with imaging examinations such as CT [70].

Another large population study [71] showed that patients with pruritus develop 13% more

Table 46.3 Other paraneoplastic dermatoses [1, 4, 78]

Paraneoplastic manifestation	Clinical characteristics	Associated neoplasias	Comments
Scleromyxedema	Papules with a waxy aspect, symmetric on the face, MsSs, and upper chest. Leonine facies due to mucin deposition. Systemic manifestations	IgG-A type monoclonal (meaning not determined)	Are associated neoplasias iatrogenic because melphalan was used?
		Multiple myeloma, leukemia, non-Hodgkin lymphoma	
		Hodgkin's disease	
Scleredema	Indurated edema of the cervical region and upper back. It may progress to disseminated hardened sclerosis	Lymphoma	Often associated with diabetes mellitus
		Myeloma	
Amyloidosis	Purpura in the region of the upper eyelid, face, and neck	Monoclonal gammopathy	The amyloid substance is positively stained with Congo red and greenish birefringence is observed under polarized light
		Multiple myeloma	
	Waxy papules in a region of flexures, eyes, and retroauricular	Multiple endocrine neoplasia (MEN)	
	Macroglossia		
	Carpal tunnel syndrome		
Vasculitis	Palpable purpura on MsIs	Lymphoproliferative diseases (lymphomas, Hodgkin's disease, leukemia)	Rarely associated with malignant neoplasm
Cryoglobulinemia	Purpura	Multiple myeloma	Characterized by the precipitation of immunoglobulins and cryoglobulins in the blood vessels, induced by the cold
	Ischemic ulceration	Waldenstrom's macroglobulinemia	
	Livedo reticularis		
	Acrocyanosis	B-cell neoplasias	
	Raynaud's phenomenon		
	Arterial thrombosis		
Carcinoid syndrome	Episodes of flushing in the face, cervical region, and upper trunk	Carcinoid tumor (endocrine cells of the small bowel) outside the GIT or metastatic to the liver	Diarrhea
			Bronchospasm
	Telangiectasias		Diagnosis: 5-hydroxyindolacetic acid in urine
	Pellagra type lesions		
Cushing syndrome	Obesity (?)	Anterior pituitary tumor	There may be no presence of obesity
	Hyperpigmentation		
	Acne, striae, telangiectasia, ecchymoses	Carcinoma of the lung	Hyperpigmentation is a common finding in patients with neoplasia
		Carcinoid tumor	
	Proximal muscle weakness	Carcinoma of the thymus, pancreas, thyroid	Late manifestation of the tumor
	Hypertension, hyperglycemia		
		Pheochromocytoma	
	Hypokalemia	Neoplasias of the male and female reproductive tract	
Pityriasis rotunda	Well-demarcated, circular desquamative plaques of the hypo- or hyperchromic type	Hepatocellular carcinoma, stomach, esophagus, palate, prostate	Rare
			Associated with non-neoplastic diseases: tuberculosis, Hansen's disease, and pulmonary disease
	Generally on the trunk	Lymphocytic leukemia	
	No pruritus	Multiple myeloma	

MsSs upper limbs, *MsIs* lower limbs, *GIT* gastrointestinal tract

malignant neoplasias, hematologic or solid. The greatest risk of cancer diagnosis occurred in the first 3 months of follow-up of the pruritus (RR 2.14, 95% CI 1.67–2.70) dropping to a risk of 1.42 (95% CI 1.19–1.68) in months 4–12 of follow-up. After 12 months of follow-up, the relative risk becomes close to that of the general population. Even so, the authors do not recommend extensive investigations of patients with pruritus [71].

The pathogenesis of paraneoplastic pruritus is still unknown. One of the hypotheses studied is an increase in cytokines (IL-6, IL-8, IL-31) potentiating the T-helper 2 (Th2) response, similarly to what happens in atopy. The tumoral T lymphocytes present a high expression of IL-31 in patients with pruritus who have lymphoma [4, 72].

The treatment of PP is to treat the malignancy when present. Several substances can be used to reduce the symptoms: hydroxyzine, paroxetine, naltrexone, mirtazapine, doxepin, amitriptyline, and others [65].

Erythroderma

Erythroderma is a condition characterized by generalized erythema and scaling, often associated with pruritus (Figs. 46.14, 46.15, and 46.16) [4]. There may be systemic manifestations such as fever, generalized adenopathies, high-output heart failure, and hypoalbuminemia [4, 73, 74].

It is usually more prevalent in males (2–4:1) and the age of onset of the symptoms is 40–50 years [73–75]. The great majority of cases is associated with the presence of pre-existing dermatoses, such as psoriasis, atopic dermatitis, and pityriasis rubra pilaris, or with the use of medications [73, 74, 76, 77]. Moreover, the reaction can be considered idiopathic in up to 50% of the cases [76, 77].

The prevalence of neoplasia in patients with erythroderma varies from 2% to 11% [73–75]. The most often associated neoplasias are lymphomas and leukemias. In the majority of case

Fig. 46.14 Erythroderma: generalized erythema and scaling

Fig. 46.15 Erythroderma: generalized erythema and scaling. Erythroderma, more closely

series the most frequently associated neoplasia is cutaneous T-cell lymphoma [73, 75]. However, in these patients erythroderma is considered one more direct manifestation of tumor invasion rather than a paraneoplastic dermatosis [76].

Fig. 46.16 Erythroderma: generalized erythema and scaling. Hands in detail

Among the solid tumors there are reports of the association with cancer of the tongue, liver, lung, stomach, thyroid, and prostate [78].

The histopathologic examination tends to be nonspecific, with acanthosis and hyperkeratosis associated with chronic lymphocytic inflammatory infiltrate, primarily perivascular [76].

The treatment of erythroderma depends on the treatment of the underlying disease when present [76]. Once the neoplasia has been diagnosed it must be treated. Treatment can be aimed at relief of the symptoms with baths, emollients, and topical corticotherapy. In addition, it is necessary to consider the general state of these patients, their hydroelectrolytic balance, and the development of secondary infections [78].

Genetic Syndromes Associated with Malignant Neoplasias and Cutaneous Manifestations (Table 46.4)

These constitute cutaneous manifestations of inherited syndromes that are more susceptible to malignant neoplastic diseases. Since the cutaneous manifestations do not reflect the course of associated neoplasias, they do not fit the definition of paraneoplastic syndromes defined by Curth [77].

Table 46.4 Genetic syndromes associated with neoplasias and skin [79, 80]

Syndrome	Cutaneous manifestations	Associated tumors	Comments
Cowden syndrome (multiple hamartomas)	Brownish papules on the face, neck, tongue, and gingiva (trichilemmomas)	Breast	Autosomal dominant
		Thyroid	Predominates in women
		Endometrium	
	Punctate keratosis	Gastrointestinal polyps	Mutation in the tumor suppressor gene *PTEN/MMAC1* present in chromosome
	Papules on the back of the hands		10q22–23 (codes the tyrosine phosphatase protein that regulates cell proliferation)
	Lipomas		
	Hemangiomas		
Gardner	Epidermoid cysts, fibromas, lipomas, leiomyomas, trichoepitheliomas, neurofibromas	Adenomatous polyps in the gastrointestinal tract (colon and rectum)	Autosomal dominant
			Associated with the tumor suppressor gene APC (adenomatous polyposis coli) in chromosome
	Osteomes (membranous bones of face and head)	Thyroid	5q21–q22. Involved in cell migration and cell cycle control
Peutz–Jeghers	Pigmented maculas (ephelide type) on the lips, nose, oral mucosa, subungual	Extensive hamartomatous polyps and carcinomas of the gastrointestinal tract, especially the small bowel	Autosomal dominant
			Extensive hamartomatous polyps and gastrointestinal tract carcinomas, especially of the small bowel
		Appears to have a higher risk of cancer of the pancreas, breast, cervix, ovary, and testicles	Mutation in tumor suppressor gene *STK11/LKB1*
			In the chromosome
Muir–Torre	Tumors of sebaceous glands, malignant and benign (generally on trunk), keratoacanthomas	GIT neoplasias	Autosomal dominant
		Hematologic cancer	Part of the nonpolyposis syndrome of hereditary colon cancer
		Genitourinary	
		Breast	Mutation of gene MSH-2, located in chromosome 2p22–p21, and MSH-1, located in chromosome 3p21.3
Howel–Evans	Palmoplantar hyperkeratosis	Esophageal cancer	Hyperkeratosis begins in childhood
	Oral leukoplakia		Gene TOC located in chromosome 17q25
Birt–Hogg–Dubé	Skin tags	Renal carcinoma	Mutation of gene17p11.2 codes for folliculin
	Fibrofolliculomas and trichodiscomas on the face and neck		Higher incidence of pulmonary cysts and spontaneous pneumothorax
Hereditary leiomyomatosis/renal cell cancer syndrome	Cutaneous leiomyomas with segmental or strip distribution (not diffused and symmetric) around 25 years	Papillary renal carcinoma (rapid evolution to lymph nodes and bad prognosis)	Autosomal dominant
			Uterine leiomyomas
			Mutation of gene that codes fumarate hydratase. Mapped in gene 1q42.3–43

Syndrome	Clinical features	Associated neoplasms	Genetics / notes
Melanoma/pancreatic cancer syndrome (familial atypical multiple mole melanoma-pancreatic cancer syndrome)	Multiple atypical nevi	Pancreatic cancer Melanoma	Mutation in gene CDKN2A in chromosome 9p21
	Increased incidence of melanoma	Breast cancer	
Multiple neuroma syndrome (multiple endocrine neoplasia, MEN type 2B)	Multiple neuromas that appear as whitish nodules on the lips and anterior third of the tongue. They may also appear on the oral mucosa, gingiva, palate, pharynx, conjunctiva, and cornea	Medullary carcinoma of the thyroid	Rare Autosomal dominant
	Protuberant lips	Pheochromocytoma	Hyperparathyroidism Mutation in tyrosine kinase receptor (RET) proto-oncogene in chromosome 10
Type I neurofibromatosis	Axillary and inguinal ephelides, café-au-lait macules, cutaneous neurofibromas, plexiform neuromas	Schwann cell tumors Malignant degeneration of neurofibromas Pheochromocytomas Optic glioma	Autosomal dominant Mutation in gene NF-1 in chromosome 17q11.2 (produces neurofibromin, a tumor-suppressor protein)
Ataxia-telangiectasia syndrome (Louis–Bar syndrome)	Telangiectasias of the conjunctiva, auricular pavilion, palpebrae, malar region, antecubital and popliteal and presternal fossae	Lymphoid tumors (risk 100 times greater than in the general population)	Autosomal recessive Ataxia (2–3 years of age) Immunodeficiency (diminished or absent IgA, IgE, and IgG2) Risk of developing tumors is 37 times greater than in the general population
		Leukemia	
		Lymphoma	Mutation in gene ATM in chromosome 11q22–23 which signals damage in DNA
Bloom's syndrome	Café-au-lait macules, photosensitivity (center facial erythema), Small stature, thin facies, photosensitivity	Leukemia Lymphoma Gastrointestinal adenocarcinoma	Defective gene in DNA helicase (RECQL3) which reduces chromosome stability and the DNA repair capacity
Rothmund–Thomson syndrome (congenital poikiloderma)	Photosensitivity with striated erythema in the first year, telangiectasias, depigmentation and atrophy of the face, extensor extremities, and buttocks (poikiloderma), alopecia	Basocellular and spinocellular carcinomas Osteosarcoma Fibrosarcoma, non-Hodgkin lymphoma Thyroid adenoma Gastric carcinoma	Defective gene in DNA helicase (RECQL4) which reduces chromosome stability and the DNA repair capacity
Wiskott–Aldrich syndrome	Petechiae, ecchymoses, eczemas, bacterial infections	Neoplasias, lymphoreticular (Hodgkin lymphoma and B cells)	Gene WAS chromosome Xp11

Glossary

Acanthosis   Thickening of the spinous layer. It is a type of epidermal hyperplasia.

Acrokeratosis   Clinical condition characterized by erythematous to violaceous papulosquamous plaques arise over accrual areas.

Erythema gyratum repens   Disorder characterized by the presence of polycyclic, serpiginous erythema with scaling on its border, rapidly progressive, producing ring-shaped erythematous, concentric figures similar to a wood surface. It is highly associated with neoplasias.

Erythroderma   A condition characterized by generalized erythema and scaling, often associated with pruritus and systemic symptoms

Hamartoma   A benign tumor-like malformation composed of an abnormal mixture of mature cells and tissues found in areas of the body where growth occurs. It is considered a developmental error and can occur at a number of sites. Example: hemangiomas, melanocytic nevi.

Hypertrichosis   Increase in density and length of the hair accepted limits of normal for age, sex, or race.

Ichthyosis   Prolonged retention of the stratum corneum, leading to the formation of fishlike scales.

Interleukins   Low molecular weight molecules (cytokines), important intercellular messengers, produced by leukocytes, which preferably exert their effect in other white blood cells.

Leiomyomatosis   State of having multiple benign tumor of smooth muscle (leiomyomas).

Leser–Trélat sign   Sudden increase in the quantity and rapid growth in size of seborrheic keratoses.

Multiple endocrine neoplasias   Rare, inherited genetic mutational disorders whereby several endocrine glands develop benign or malignant tumors or grow excessively without forming tumors. A single gene responsible for type 1 disease has been identified. Abnormalities in a different gene have been identified in persons with types 2A and 2B disease.

Necrobiotic xanthogranuloma   A disease caused by a granulomatous inflammation that results in the presence of plaques and firm, yellowish nodules, particularly in the face.

Necrolytic   Describes processes occurring in cell necrosis and tissue detachment.

Pachydermatoglyphy   Palmar thickening with marked palmar ridges and grooves, which exaggerate the dermatoglyphs (digital print) giving it a rough, velvety appearance.

Paraneoplastic disease   Clinical or biochemical alterations associated with malignant neoplasias that are not directly related to the invasion of the primary tumor or its metastases.

Poikiloderma   Descriptive term that combines atrophy, telangiectasia, and hyper- or hypopigmentation that may occur in different clinical situations.

Reticulohistiocytosis, multicentric   Systemic granulomatous disease of unknown cause. Papulonodular skin lesions containing a proliferation of true histiocytes (macrophages) are associated with arthritis.

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Psychiatric Diseases

47

Cecilia Cassal and Ygor Ferrão

Key Points
- Psychodermatology studies the cutaneous manifestations that derive from triggering and aggravating mental factors, and social prejudice and emotional damage resulting from this interaction.
- Skin-related complaints represent 10–58% of primary consultation reasons in general healthcare units in Brazil and North America.
- Self-inflicted dermatosis most prevalent are neurotic excoriation, artifact dermatitis, trichotillomania, delusional parasitosis, and body dysmorphic disorder.
- Lack of control impulse generated by imbalance in serotonergic, noradrenergic, and dopaminergic neurotransmitters and defects in the opioid systems are possible etiologies for psychodermatosis.
- Psychiatric drugs for the treatment of psychodermatosis include selective serotonin reuptake inhibitors, antipsychotics, and mood stabilizers.
- The multifactorial aspects of psychocutaneous diseases require transdisciplinary approach.

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Epidemiology

The most widely accepted definition of health care refers to a comprehensive approach of individuals in their physical and psychosocial aspects. Embryology explains the common ectodermal origin of the central nervous system and the skin, the largest organ of the human body. With a physiology related to metabolism, thermal and immune modulation, neurosensory perception, and the psyche as a structural border of personality between what is conceived as self and the outer environment, the skin is the first visible aspect of the persona, where it plays a role of social interface, with implications for issues of socialization, self-esteem, and life relationships. The territory of dermatology, psychiatry and psychology, neurology, and endocrinology, the skin

demands a multidisciplinary approach. Psychodermatology studies the interaction between skin and psychosocial factors.

Skin-related complaints represent between 10% and 58% of reasons for primary consultation in general healthcare units in Brazil [1] and North America [2]. Among these patients, 4–10% need to be referred to a specialist [3–5], which means, conversely, that 90% of patients not advised to see a referral service will be managed by primary healthcare professionals. The prevalence of psychological distress/emotional pain in patients with dermatologic disease may reach 25% [6]. A third part of consultations involving the skin as a major complaint corresponds to diseases that keep interfaces with dermatology and mental health: psychodermatoses [7]. The challenge to the general practitioner as a first medical contact at the healthcare network, and to the dermatologist, for being referred to as a specialist, is – considering such conceptions and demands – to treat the most prevalent dermatosis properly.

Classification and Diagnosis: Dermatology and Psychiatry Approaches and Systematization of Studies

Dermatology

Psychodermatology has been studied with greater emphasis since the 1950s, and in the 1970s the mechanism by which emotions affect the physical body was unraveled [8]. Several authors, such as Koblenzer [9] and Koo [10], classified the psychocutaneous disorders. The different classifications were adapted into six categories in order to systematize the study of psychocutaneous interfaces:

I. Psychophysiologic disorders, whereby a primary cutaneous disease may be exacerbated by emotional factors and stress, such as psoriasis and atopic dermatitis.

II. Primary psychiatric diseases, whereby the patient does not have skin pathologic substrate and all findings are represented by self-induced lesions, as in delusional parasitosis, artifact dermatosis, neurotic excoriation, trichotillomania, and onychophagy.

III. Secondary psychiatric disorders, which occur when the patient develops psychological problems as a consequence of a skin disease that causes physical disfigurement, such as vitiligo and alopecia areata. Difficulties adapting to these disfiguring conditions may be related to depression, anxiety, and the development of social phobia [11].

IV. Cutaneous sensory disorders, whereby the patient presents with purely sensory complaints, such as itching (pruritus), burning, or tingling, with no evidence of skin disease or other underlying medical condition.

V. Conditions related to the use of psychoactive drugs for the treatment of primary dermatologic diseases, such as (a) administration of doxepin for treatment of chronic urticaria or amitriptyline for postherpetic neuralgia [9, 12]; (b) cutaneous effects due to the use of drugs necessary for the treatment of psychiatric disorders, such as acne and psoriasis related to lithium use; and (c) psychological manifestations, such as psychoses and depression, due to the use of dermatologic drugs, for example, corticoids or interferons.

VI. Multifactorial diseases, such as those whereby psychoneuroimmunologic factors play a synergistic role in triggering or aggravating the cutaneous condition, are exemplified by atopic dermatitis, psoriasis, lichen planus, chronic pruritus, chronic idiopathic urticaria, angioedema, and alopecia areata [13]. The role of stress, as well as psychoneuroimmunology, has been widely investigated, as has the genesis of the psychodermatosis (Box 47.1).

Psychiatry

In the chapter regarding the classification of mental disorders and behavior of the *International Classification of Diseases*, in its 10th edition (ICD-10) [15], Impulse Control Disorders are called Habit and Impulse Disorders [F63] and are inserted in the Section of *Disorders of Adult Personality and Behavior* (F60–F69). It is observed that the disorders are grouped by descriptive similarities and not by the knowledge that they share any other important aspects. The ICD-10 defines disorders as characterized by repetitive actions that do not have any clear rational motivation and that, usually, jeopardize both private and third parties' interests. Such behavior is associated to impulses or actions that cannot be controlled. Importantly, the ICD-10 points out that, for conventional reasons, Habitual Excessive Use of Alcohol or Drugs (F10–F19) and Habit (and Impulse) Disorders involving sexual behavior (F65) or eating behavior (F52) are excluded from this diagnosis group [15].

The ICD-10 describes as major Habit and Impulse Disorders: Pathologic Gambling, Pathologic Incendiary Behavior (pyromania), Pathologic Stealing (kleptomania), and Trichotillomania, inserting Neurotic Excoriation and Intermittent Explosive Disorder into Other Habit and Impulse Disorders.

Until 2013, the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition* (DSM-IV) placed Impulse Control Disorders (not classified in other chapters) in one chapter where disorders that are characterized essentially by failure to resist to an impulse or temptation of performing an act that is risky to oneself or to others were included. It pointed out that most patients with these disorders experience either impending tension or excitement before performing the act. Afterward, some patients might feel regret, self-recrimination, or guilt, while others will experience pleasure, gratification, or relief [16].

The main disorders described by the DSM-IV were: Intermittent Explosive Disorder (aggressive impulses that may result in violent assault or destruction of property); Kleptomania (impulse to steal objects that are not necessary for one's personal use or are not worth in terms of financial value); Pyromania (incendiary behavior that results in pleasure, gratification, or tension relief); Pathologic Gambling (maladaptive, recurrent, and persistent behavior related to gambling); Trichotillomania (impulse of pulling and/or plucking one's hair, causing noticeable hair loss); and Impulse Control Disorder with no other specification, where repetitive acts of self-mutilation, onychophagy, oniomania (compulsive shopping), compulsive sexual behavior, and neurotic excoriations could be included.

Besides these disorders, the DSM-IV points out that the occurrence of uncontrolled impulses may occur in other diagnosis categories, such as Substance Related Disorders, Paraphilia, Antisocial and Borderline Personality Disorders, Behavioral Disorders, Schizophrenia and, in some cases, even Mood Disorders, but in the latter the Impulse Control Disorder diagnosis would be secondary [15].

After a series of publications [17–20], some Impulse Control Disorders were moved into other chapters of the DSM-5 [21]. For example, Trichotillomania and Neurotic Excoriation were moved to the group of Obsessive–Compulsive Spectrum Disorders.

Psychodermatosis: Clinical Presentation

Dermatologic

Based on the classification of dermatosis caused primarily by a psychiatric disease, this chapter approaches the skin manifestations of self-inflicted dermatosis, important motivations for either general medical or dermatologic consultation.

Neurotic Excoriation
Artifact dermatitis
Trichotillomania
Delusional parasitosis
Body dysmorphic disorder

The exclusion of other psychiatric or organic diseases, acknowledging or denying the authorship of self-injury, the possibility of impulse control or ritualistic behavior, the intention of anxiety relief or the existence of other secondary gain, and the manifestation of other perceptual issues, such as the presence of delusion, are important factors in determining the diagnosis and the therapeutic approach.

Neurotic Excoriation

Synonyms: skin picking, self-mutilation, dermatotillomania, psychogenic excoriations (Box 47.2).

Box 47.2 General Characteristics of Neurotic Excoriation
- More frequent in middle-aged females
- Affects 2% of all dermatologic patients and up to 10% of those with pruritus complaint
- Scratching, scraping, rubbing, or skin picking urges, acknowledgement of the act, and difficulty in controlling the impulse
- Frequently linear lesions, at various stages, simultaneously
- The middle of the back is typically spared

Epidemiology

Predominantly on females, it has an estimated frequency in 2% of dermatologic patients and in up to 10% of patients with pruritus complaint [22]. Although this condition may occur at any age, more severe and recalcitrant cases have their onset between the third and fifth decades of life [23].

Neurotic excoriations are characterized by repetitive skin scratching because of irritation, sensitivity changes, or benign irregularities on the skin surface, and may adopt obsessive–compulsive ritualistic aspects in some patients. Unlike factitious dermatitis, in neurotic excoriation patients recognize that the lesions are provoked by their self-inflicted acts, although they fail when trying to control such behavior. Gupta [24] describes that the psychiatric disorders most frequently associated with the manifestation of a perfectionist and obsessive personality structure, the obsessive–compulsive disorder, depression, and psychosocial stressors, exacerbate the symptoms in 33–98% of the cases.

Clinical Features

Self-provoked lesions present characteristics of linear trauma, and lesions at several stages may coexist simultaneously, ranging from scars, residual postinflammatory hyper- or hypochromia, erosions, or ulcers. Typically the middle of the back is spared, except when the patient uses tools and not only the nails to reach them. Histopathology is consistent with repetitive local skin trauma [25].

Differential diagnosis should be carried out to exclude other mental disorders, such as borderline personality disorder (frequently associated with suicidal thoughts, dissociation, impulsivity, and aggression) [8], other dermatosis that could cause pruritus, and the use of systemic medication or drugs (Picture 47.1).

Dermatologic compulsions are psychopathologic disorders characterized by a repetitive and uncontrollable impulse to perform certain actions, failed attempts to resist the urge, and increased excitement or tension immediately before the act and pleasure or gratification afterward [26] (Box 47.3).

Fig. 47.1 Patient with neurotic excoriations (Photo: personal collection)

Box 47.3 Dermatotillomania (Dermatotilexomania)

Most psychocutaneous findings reported in children do not fit properly the concepts originally created for the adult population. In this population, the term dermatotillomania is suggested for events whereby the impulse to cause or aggravate one's own skin lesions tends to manifest during times of stress or anxiety. The most frequent clinical forms are erosions on the sides of the nails by tearing, cuticle trauma, nail-fold bleeding, and excoriations in acne lesions. Eventually such behaviors may be associated with dermatophagia, i.e., swallowing of avulsed skin fragments. Onychophagy (titillomania), trichotillomania, and trichophagia have increased frequency, and special events in childhood should draw the attention of the clinician to the possibility of situations of child abuse and family psychopathology, such as Munchausen by Proxy [26, 27] (Table 47.1, Picture 47.2).

Table 47.1 Diagnostic criteria of neurotic excoriation in ICD-10 and DSM-5

ICD-10	DSM-5
Recurrent behavior of harming or excoriating the skin, resulting in noticeable injuries	Recurrent skin picking, resulting in lesions
Sensation of tension increasing, immediately before harming the skin or when the individual tries to resist the behavior	Repetitive attempts to reduce or stop skin picking behavior

Table 47.1 (continued)

ICD-10	DSM-5
Pleasure, satisfaction, or relief when harming the skin	Skin picking behavior causes clinically significant distress or impairment in social, professional, or other important areas of one's life
The disturbance is not better accounted for by another mental disorder and is not caused by a general medical condition (e.g., a dermatologic condition)	Skin picking behavior is not due to physiologic effects of substance use (e.g., cocaine) or to another medical condition (e.g., scabies)
The disturbance causes clinically significant distress or social or occupational impairment as well as impairment in other important areas of one's life. Symptoms may be circumstantial, i.e., appear in childhood or adolescence and disappear with time. The habit of damaging the skin [C1] in a state of increasing anxiety usually does not qualify for a diagnosis of Trichotillomania	Skin picking behavior is not better accounted for symptoms of another mental disorder (e.g., delusions and tactile hallucinations related to a psychotic disorder, attempts to improve a defect or noticeable failure in appearance in body dysmorphic disorder, stereotypes in stereotypic movement disorder, or intent to harm oneself in nonsuicidal self-injury)
Some individuals may present aspects of Neurotic Excoriation, but the resulting skin injury may be difficult to detect when very mild	
In these situations, it is necessary to consider whether the individual experiences or presents more significant psychological, social, or occupational distress. In some cases, after medical consultation with a specialist, the patient undergoes a medical treatment because of the frequency or the damage caused	

Fig. 47.2 Dermatotilexomania: secondary infections are frequent complications in self-inflicted injury spots (Photo: personal collection)

Artifact Dermatitis

Synonym: *factitious dermatitis* (Box 47.4)

> **Box 47.4 General Characteristics of Artifact Dermatitis**
> - Predominance in females
> - Higher incidence in late adolescence and early adulthood, but occurs in elderly patients (loneliness, need for attention)
> - Onset after stressor event
> - Self-inflicted skin lesions are often induced by objects
> - Typically located in areas within easy reach of hands
> - Assess substance abuse, other compulsions, and suicide risk

Although patients typically deny, partially or fully, their participation in the origin of injuries, artifact dermatitis is characterized by lesions caused by the use of nails, sharp objects, lit cigarette butts, or chemicals. The disease is associated with personality disorders and occurs predominantly in females [28]. Although described in

elderly patients in response to loneliness, losses, and need to obtain attention, the highest incidence is concentrated in late adolescence or early adulthood, as an unconscious response to psychological distress, stress, or as an attempt to a secondary gain [29]. Problems in keeping interpersonal relationships reflect patients' difficulties in controlling self-image and mood control, and self-mutilation behavior develops as a cry for help in response to the stress associated with poorly developed adaptive responses, associated with feelings of emptiness and anger. Sneddon (1975) describes that appearance rate of injuries after situations that cause severe stress such as diseases, accidents, and deprivation was 19–33%, and that lesions disappeared after termination of the stressor event. Besides skin self-mutilation, patients with borderline personality disorder are prone to suicide, substance abuse, or compulsive eating [30].

Clinical Presentation

Lesions typically stand out from normal surrounding skin, with exact geometric edges and bizarre aspect, which may resemble many skin diseases. Obsessive–compulsive disorders, depression, psychosis, mental retardation, and Munchausen syndrome are among the psychiatric disorders that follow artifact dermatitis [31, 32]. Peculiar appearance of lesions, associated with patient's inability to explain how they were formed or evolved, facilitates diagnosis [33] (Picture 47.3).

Trichotillomania

Synonyms: Trichotemnomania, trichoteiromania, scratching-pseudoalopecia, trichocryptomania (Box 47.5).[1]

> **Box 47.5 General Characteristics of Trichotillomania**
> - Most frequent in children and young adults
> - High rate of psychological comorbidities (depression and obsessive–compulsive disorder)

Fig. 47.3 Artifact dermatitis. Several primary lesions and linear ulceration in areas accessible to the hands. Several scarring lesions of previous events are observed (Photo: personal collection)

> - Exclude alopecia areata, fungal infections, and other itchy scalp disorders
> - Dermoscopic and anatomic pathology tests are elucidative
> - Always consider possibility of trichophagia and evaluate risk of trichobezoar

The term "trichotillomania" derives from the combination of the Greek words *trichos* (hair), *tillein* (pull), and *mania* (impulse). Therefore, trichotillomania is defined as the irresistible impulse of pulling the hair, followed by relief [34]. Trichophagia is the act of swallowing hair after avulsion. The most common self-aggressive acts are trichotillomania, trichotemnomania, trichophagia, trichoteironamia, scratching-pseudoalopecia, trichocryptomania, trichorrhexomania, and neuropathic plica, as shown in Table 47.2 [35].

Epidemiology

With an estimated prevalence of 1–2% of the general population, the disease has the highest

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[1]In this case, synonymia is given by cause-effect approximation – habit control disorder leading to hair behavior.

Table 47.2 Diagnosis features of main compulsive trichosis

Compulsive trichosis	Meaning and clinical features
Trichotillomania	Compulsive act of pulling out the hair, especially from the parietal region and vertex [37], though hair from any part of the body can also be involved in the process. Because of its diffuse characteristics and not being usually the patient's main complaint, hair thinning is often clinically perceived when it affects 30% of a given capillary area [35]
Trichotemnomania	Presence of tonsured areas within a few millimeters of the scalp surface. Hair is cut vertically, with a sharp object. Trichogram, pathology, capillary density within normal limits. Dermatoscopy or common optical microscopy allows observation of cut small and vertical hair. Unlike trichotillomania, trichotemnomania only occurs in older adults, and all cases reported are in psychopathic patients
Trichophagia	Compulsive hair swallowing behavior. Patients with long hair usually put amounts of hair in the mouth and keep chewing them, sometimes swallowing a few. A different form consists of the patient pulling hairs, typical behavior of a trichotillomania, and then taking them to the mouth. Whenever there is a clinical picture of trichotillomania, hair swallowing should be hypothesized. It may result in a trichobezoar
Trichoteiromania Tonsure trichoclasia Scratching-pseudoalopecia	Two-centimeter-long hairs and split, brush-shaped distal extremities. Erythematous and scaly scalp surface is a consequence of scratching. Pathologic anatomy may reveal acanthosis, orthohyperkeratosis, focal parakeratosis, and intraepidermal microvesiculation. Trichoptilosis, trichorrhexis nodosa, incomplete fractures and folds. Trichogram is normal
Tonsure trichotillomania	The terms trichoteiromania, tonsure trichoclasia, tonsure trichotillomania, and scratching-pseudoalopecia represent the same clinical entity. They may all be identified either on the scalp or other region where there is friction, as in the pruritic dermatosis such as lichen planus, atopic dermatitis, or neurodermatitis
Trichokryptomania or trichorrhexomania	The terms trichokryptomania and trichorrhexomania are synonymous and correspond to a compulsive act of cutting the hair with the nails, which can occur either close to the scalp or several centimeters from skin surface. Usually there is no area of alopecia but hairs cut into various sizes, resembling a "bad hair day." The hairs present on their distal end a brush-like appearance. Trichotillomania (pull out) can be concurrent
Neuropathic plica	In psychiatric patients, the presence of too tangled hair, leading to formation of a hardened mass. Differential diagnosis with acute compression of the hair, electrostatic phenomenon that occurs in the hair during washing

Source: Organized by the authors, after a review by Pereira [35]

incidence in children aged 4–10 years, adolescents, and young adults [26], with an incidence of 3.4% in women and 1.5% in men. In the United States, 2–8 million people may have trichotillomania, with 90% being women and 0.6% students; 43% of patients deny the act of pulling the hair [36]. Overall, 40% of cases are not diagnosed and 58% of patients are untreated. In childhood, trichotillomania is seven times more frequent, with an average age of 8 years for boys and 12 for girls [27, 34].

Etiology

Despite variable etiology describing a simple habit reaction to stress and anxiety, the comor-bidity rate with other diseases is high, the most frequent being obsessive–compulsive disorder and depression. Delusions may be associated with trichotillomania. Other symptoms of anxiety can be evidenced by the presence of onychophagy and onychotillomania, suggesting evaluation for diagnosis of obsessive–compulsive disorder.

Clinical Presentation

Frontotemporal regions of the scalp, eyebrows, eyelashes, beard, and pubic hairs are usually affected; pubic hairs may or may not be sucked and swallowed [36]. Typically, hairs in the affected area have different lengths and the

tensile test is negative on peripheral area. Dermatoscopy shows decreased capillary density, hairs broken in different sizes, yanked hairs, vellus, trichoptilosis, and yellow dots with or without black dots [37, 38]. Differential diagnosis should be performed considering alopecia areata, tonsuring tinea, and pruritic dermatosis of the scalp, such as lichens. The lack of typical hair in club (exclamation points) and mycologic test when fungal infection is suspected will exclude these etiologies.

Trichotillomania is one of the rare psychodermatoses is characteristic in hair histopathology, where trichomalacia, characterized by the presence of blackened impregnations (rods remains) in follicular ostia, is only observed in these patients [35, 36]. Pigmentary remains close to follicle isthmus, follicles destroyed by perifollicular hemorrhage, several empty follicle channels, dilated hair follicle infundibulum, and corneal stoppers may also be seen, mostly in the catagen phase or initial anagen without perifollicular inflammatory processes [35]. Trichoptilosis, pili torti, and trichorrhexis nodosa are observed by dermatoscopy. In the semiologic analysis of trichotillomania, other tests described by Pereira [35] are: negative gentle traction test, since most hairs are in anagen phase, not falling off easily. In this test, a breaking damaged hair shaft can produce false positives; the hair pull test, which implies intense hair traction, obtaining fragments, demonstrating hair fragility; and the friction test, which consists of placing a hair pad in the center of the palm of one hand and rubbing it with the finger, obtaining pieces of the hair damage, typical of hair shaft lesion. Trichogram can result in up to 100% of hairs in anagen phase, as telogen hairs are first extracted because they have lower adhesion to the follicle and its extraction is less painful; thus, whole hair restoration is anagen. Analysis of spontaneously eliminated hair, collected by the patient's companion without his knowledge, in places where he has been, and those brought by the patient himself, usually a small sample to justify possible denial and lack of interest in cooperating with the doctor, will reveal the presence of anagen, catagen, or telogen hair with epithelial bag, showing that hairs were extracted by traction. Hair coat study consists of observing small hairs with the aid of a paper card placed perpendicularly to the scalp and removing a sample of them. According to Pereira [35], a hair plucked in the anagen phase results in three possible findings: (a) hair breaks close to the root but will continue to grow soon; (b) hair is fragmented inside the follicular channel and, in this case, may form the trichomalacia; and finally, (c) hair breaks off a few centimeters from scalp surface. Such a test is important for differential diagnosis of androgenetic alopecia, wherein drawn hairs will be predominantly telogen. The fluorescent light test consists of using fluorescent ink (such as text marker pens) close to modified scalp area. Examination of the patient's fingers with a Wood's lamp on the day after will show fluorescence. In the observation window technique, a small area of hair is cut close to the scalp and isolated with scotch tape. This feature will show the patient normal growth of his companion hair (Box 47.6).

Box 47.6 Trichobezoar

Trichobezoar occurs in 90% of cases in girls with long hair. Presence of weight loss and imprecise gastrointestinal manifestations should draw attention to the possible diagnosis. Clinically, vomiting and nausea can be observed in 64% of patients, abdominal cramping in 70%, changes in bowel habit in 32%, palpable epigastric mass in 88%, as well as other gastrointestinal disorders. It is often related to the presence of mental retardation. Mortality rate by trichobezoar may reach 50% if there is no early diagnosis with treatment [35] (Pictures 47.4, 47.5, and 47.6).

Fig. 47.4 Patient with extensive alopecic area caused by hair pulling (Photo: personal collection)

Fig. 47.5 The same patient may pull out hair from more than one site of the body (Photo: Paula Baldissera Tansini collection)

Fig. 47.6 The same patient may pull out hair from more than one site of the body (Photo: Paula Baldissera Tansini collection)

Delusional Parasitosis

Synonyms: *Ekbom syndrome, acarophobia, dermatozoic delirium, psychogenic parasitosis, delirium of internal zoopathy, delusional infestation, Morgellon's disease* [39] (Box 47.7).[2]

> **Box 47.7 General Characteristics of Delusional Parasitosis**
> - Starts at the sixth decade, prevalence of one man for every three women over 50 years old
> - Irreducible belief of being infested by parasites or other foreign objects
> - Exclude psychoses induced by use of substances or drugs, organic causes, cerebrovascular disease, vitamin B12 deficiency
> - Can manifest simultaneously in persons in close contact (folie à deux)
> - Frequent medical shopping and adhesion issues

Delusional parasitosis (DP) was first reported by Darwin [40], regarding an individual who experienced a wild idea (an itch) so powerfully that it could not be changed suddenly, either by visual sense or reason. In 1894, in relation to other similar cases, Thiberge called it acarophobia, and subsequently Perin published new accounts in 1896. In 1938 the syndrome was defined by Ekbom, who described seven cases and called it *dermatozoenwanh*, dermatozoic delirium. Also known as delusional parasitosis or psychogenic parasitosis, the Ekbom syndrome is infrequent and is characterized by the patient's strong conviction that he is infested with worms that come out of the skin, usually the scalp,

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[2]*Morgellons disease is a term coined in 2002 by Mary Leitao, founder of the Morgellons Research Foundation (www.morgellons.org). With the advent of the internet, patients go researching for symptoms on the web and self-diagnose, which consists of delusional infestation, when they believe to be infested by inanimate objects, usually multicolored fibers of uncertain origin, but also food, nanotechnology products, fungi, bacteria, etc. The disease is not recognized in the scientific community, but eventually became a mass phenomenon – the first disease "transmitted" via the internet.*

mouth, eyes, or genital area [41, 42]. Dupré described a *délire de zoopathie interne* (delirium of internal zoopathy) and Levy subdivided it into "internal" and "external" types [43]. The main characteristic of these syndromes would be the delusional belief (*délire*) of harboring animals in the body or on the body. The 29 cases described by the author involved rats, birds, worms, snakes, and so forth, but insects were not mentioned. Faure et al. [44], in turn, described two cases in which *le délire zoopathique* involved insects and reiterated the idea that the fundamental problem was "delusional" in its nature. Wilson and Miller [45] suggested the term "delusional parasitosis" and favored their delirious origin. The emergence of other specimens mentioned by patients as responsible for skin symptoms, such as fibers and nanotechnology products, led Freudenmann and Lepping (2009) to advocate the use of the term delusional infestation [39].

With an approximate prevalence of 83.21 affected individuals per million population, the syndrome starts predominantly in the sixth decade, with an average age at onset of 55.6 years [47]. Lyel (1983) describes a male to female ratio of 1:1 in those under 50 years of age and 1:3 in patients over 50. The delirium, with a paranoid character, manifests itself in between 15% and 40% of cases and may develop more often in people with obsessive traits and paranoia. Such descriptions led some authors to consider delusional parasitosis as a picture of monosymptomatic hypochondriacal psychosis [46]. In an extensive discussion on the true nature of delusional parasitosis, Ekbom studies particularly the nature of tactile sensations described by patients, suggesting an organic basis for this syndrome and questioning whether it would be a distortion of real perceptions or a hallucinatory phenomenon [47, 48].

Clinical Presentation

Onset of symptoms can be sudden and slow with complaints of rash, tickling, some feeling of movement inside the skin, tingling, or tactile hallucinations, triggering the feeling of parasitism. Although there is no typical elementary lesion, the skin disorder often found is due to excoriation and scarification, performed to remove parasites or fibers or other foreign objects that the patient believes are under the skin. Linear or oddly shaped ulcers, erosions, and scars, as well as nodular prurigo, are usually symmetric findings in hand access areas and, for this reason, the center of the back is often spared. Patients retell, obsessively, and in detail, the morphology, life cycle, and habits of these "parasites" as well as the actions taken to avoid and eliminate them. Some patients, in a hallucinatory state, collect pieces of skin, paper, or other specimens, identifying these fragments as parasites. This behavior has been termed the "matchbox sign" [49, 50] in allusion not to the means by which it is presented (matchbox, plastic envelopes, tubes, etc.) but to the agent assigned by the patient as responsible for the infestation. Replacing the classic "matchbox sign," Freudenmann and Lepping (2009) suggest the use of the term "specimen sign," since it is not unusual for patients to submit photographs or videos taken by them to verify the infestation. Sometimes people who live close to the patient (and are influenced by him) share the same feelings and beliefs. This situation is called folie à deux, shared madness [39, 48] (Picture 47.7).

Diagnosis should exclude real skin infestations and other organic, infectious, and metabolic causes, and assess cerebrovascular and psychiatric comorbidities other than monosymptomatic delirium, as well as the use of psychoactive drugs such as opioids, amphetamines, and cocaine.

Fig. 47.7 In a variation of the matchbox sign, the patient brought an insect to the medical office, to which he attributed the colonization of his wife, in a folie à deux delusional parasitosis case (Photo: personal collection)

Trichophobia is the belief of the existence of something in the root of the hair, which disappears when it is pulled off, after which normal hair may grow back. Dermatologically it may be expressed as alopecia, and differential diagnosis should pay attention to different forms of trichotillomania. The patient's belief in the presence of parasites or other foreign and non-existent objects provides clues to delusional thinking (Box 47.8).

Box 47.8 Hallucination, Delirium, and Delusion

Conceptual confusion about tactile hallucinations causes the disorder sometimes to be classified from the perspective of perception, sometimes from a cognitive point of view. Regarding a reasonable confusion among the terms hallucination, delirium, and delusion, Berrios (2011) explains that French and German psychiatry have established a less strict line between hallucinations and delusions than English psychiatry, where *"délire"* and *"wahn"* (French and German terms for delirium, respectively) share a less "intellectualist" direction than the English word *"delusion." "Délire"* and *"wahn"* assume a personality disorder and a fracture in the "relationship" between the subject and his world, which the English term *"delusion"* lacks, usually defined as a wrong or pathologic "belief" and, thus, a thought disturbance. Hallucinations, therefore, tend to be regarded as a subtype to delusions ("sensory delusions") and, as a consequence, less emphasis is placed on its aspects of "perception" than on those called "cognitive" or "apperception" aspects. Literature on descriptive psychopathology are singularly reticent about tactile hallucination, and the *Traité* by Ey devotes only 16 pages to it, out of a total of 1543 [47, 48].

Body Dysmorphic Disorder

Synonyms: Dysmorphophobia (Box 47.9)

Box 47.9 General characteristics of Hallucination, Delirium and Delusion
- May affect 10–14% of dermatologic patients
- Frequent onset in young adults
- Defined by the concern with minimal or no flaw at all in one's appearance
- Complaints often refer to the nose, mouth, hair, breasts, and genitals
- Typically associated with ritualistic or compulsive behaviors

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Clinical Presentation

In patients suffering from body dysmorphic disorder (BDD), disturbance in the perception of their own body image, usually a concern with a flaw on the face, nose or mouth, hair, breasts, and genital area, often generates social isolation and adoption of ritualistic behaviors, such as spending a lot of time in front of the mirror and checking it several times, looking for small imperfections. BDD may be manifested as olfactory reference syndrome, whereby the concern relates to an unpleasant odor emitted by the patient, not noticeable by anyone else. These patients often adopt compulsive behaviors to eliminate the perceived odor, such as bathing repeatedly or using products such as deodorants, perfumes, or mouthwashes excessively, as well as arranging multiple medical consultations rationalize their issues. The consequences of ritualistic behaviors can be dermatologic, such as eczemas caused by product contact and, occasionally, erosion in areas burned repeatedly. The spectrum of BDD includes obsessions and delusions – in this case, without the corresponding insight about the problem – which do not meet the criteria for obsessive–compulsive disorder or for the spectrum of psychoses disorders, useful classifications for treatment purposes [23]. It is estimated that BDD affects about 1% of the

United States population and that 10–14% of patients who visit dermatologists have a positive screening for BDD, with an average age around 34 years; it affects both genders equally [23, 51].

Psychiatric/Psychological

Self skin-damaging behavior can occur in response to a delusion (parasitosis), hallucination, or tactile delusion (tingling) as in a psychotic disorder, such as schizophrenia or manic episodes [52, 53]. In such cases, disorder excoriation should be diagnosed as secondary to the main disorder. In general, compulsive or excessive washing in response to contamination fears (which may be the result of any kind of obsessive content) in individuals with obsessive–compulsive disorder can lead to skin lesions [20]. Individuals with BDD may scar or pinch their own skin because of concerns about the appearance of certain body parts (e.g., nose, soles of the feet, jaw, and palms of the hands) [54]. As in psychoses, in such cases the excoriation disorder should also not be considered as a primary diagnosis. Although a stereotypic movement disorder might be characterized as repetitive behavior of self-mutilation, its onset usually occurs in early developmental period. For example, individuals with the neurogenetic condition of Prader–Willi syndrome may have an early-onset behavior of pinching the skin, and its symptoms may meet the criteria for the stereotypic movement disorder [55]. Similarly, although complex motor tics, present in patients with Tourette's disorder, can lead to behaviors of self-mutilation, this is a sudden, automatic, and uncontrollable behavior, which differs considerably from the psychopathologic viewpoint of self-harm behavior in the excoriation disorder [56]. Excoriation disorder should not be diagnosed when skin injury occurs as a consequence of misleading or simulated behavior, such as those occurring in the factitious disorder (or Munchausen syndrome) [57]. Within the heterogeneity of depressive disorders, the excoriation disorder should not be diagnosed if skin pinching is mainly attributed to the intention of hurting oneself in order to reduce psychological distress (anxiety) [58] or to play the role of a cry for help, which occurs in characterological depression, as a result of personality disorders (especially borderline and histrionic personality disorders). [59]. Although the diagnosis of excoriation disorder cannot occur when there is another medical condition present, it may be precipitated or exacerbated by an underlying dermatologic condition. For example, acne can lead to scratching and tearing, which may also be associated with the comorbid excoriation disorder. Differentiation between these two clinical conditions (acne with itching and pinching versus acne with comorbid excoriation disorder) requires an assessment of to what extent skin pinching became independent of the underlying dermatologic condition. Medications of various types (including psychotropic drugs) may also cause itching and, therefore, lead to repetitive abrasions.

Etiopathogenesis of Psychodermatosis

Little is known about which organically based factors are associated with excoriation disorder. If considered as a lack of control impulse, the most accepted hypothesis will be that there is an imbalance in serotonergic, noradrenergic, and dopaminergic neurotransmitters [18]. Modulation of opioid systems is also a possibility, as some patients with neurotic excoriation seem to have a good response to fentanyl, an opioid antagonist, contrary to what was observed in patients with trichotillomania [60], but this study was never replicated and its sample was too small to be conclusive (n = 10).

So far, there is no evidence in neuroimaging studies to substantiate the neurobiology or neurocircuits of excoriation disorder. However, by phenomenological analogy with trichotillomania (both are part of the "grooming behaviors"), it may be speculated that there are changes in the basal ganglia, particularly due to the reduction in volumes of putamen and cerebellar involvement [61].

There seems to be an intersection of the circuits involved in obsessive–compulsive disorder with those potentially involved in neurotic excoriation, but insufficiently so to consider that both are mediated by the same structures or similar neurotransmitters [62].

Psychoanalytic

Historically, individuals with psychogenic excoriation are described by psychoanalytic literature as having an obsessive–compulsive personality configuration; i.e., a rigid, perfectionist, judgmental, controlling, and indecisive personality for fear of making mistakes. These patients would rarely have contact with feelings and struggle with difficulty in dealing with unconscious aggression. This aggression would originate from unresolved feelings toward their parents. Symptoms of psychogenic excoriation are connected to the anxiety generated when aggressive manifestations reach the surface. A broad pathology spectrum is found, ranging from neurotic symptoms that appear only under stress, to the patient who is unable to act because of compulsive behavior that influences many aspects of his or her life.

Social (Family)

In some situations it can be manifested as a reaction to the pressure of psychosocial factors related to family or work, which generates a high level of stress culminating in symptoms, similar to what occurs in trichotillomania.

Treatments: Dermatologic, Psychiatric, and Psychotherapeutic

Dermatologic

Treatment should be conducted with the intention of identifying triggering factors, in association with psychiatric treatment. Lesion occlusion in order to hinder self-harm and identification of best adaptive behaviors as substitutes for self-aggression can help (for example, the use of emollient to replace the act of scarring). Early diagnosis of psychodermatosis can prevent both habit consolidation and chronicity, and severity of skin sequelae caused by injuries. Direct confrontation of the patient is not suggested [63]. Although formal training of dermatologists does not contemplate these therapeutic resources, some authors suggest that hypnosis, biofeedback, and relaxation exercises can be a useful adjunct to the therapy of psychodermatosis, associated or not with psychoactive drugs [9, 23, 64].

Psychiatric

There is no specific pharmacologic treatment for neurotic excoriation, and medicines are used to treat target symptoms or primary conditions such as depression, anxiety, or obsessive–compulsive symptoms. Main drugs used in the treatment of psychodermatosis, their dosages, side effects, and some remarks about their use are listed in Table 47.3. Only drugs that have already been submitted to a clinical trial are listed (open or randomized double-blind trials). Case reports were not considered for this review.

Selective serotonin reuptake inhibitors (SSRIs): only case reports support the use of SSRIs in patients with skin picking, but there is no robust evidence to support their use, except situations of neurotic excoriation secondary to depressive episodes, anxiety scenarios, or obsessive–compulsive disorder [18].

Antipsychotics, especially atypical antipsychotics, which have a serotonergic effect associated with dopaminergic antagonist, seem to be promising in the treatment of excoriation disorder, as well as trichotillomania [18, 65], but there are no studies with adequate methodology and sufficient sample sizes to recommend their use as definitive treatment.

Mood stabilizers (lithium and anticonvulsants): As with SSRIs, mood stabilizers may be promising, but the evidence is based on case reports, especially with the use of lithium carbonate [66].

Table 47.3 Psychiatric drugs with some evidence level used in the treatment of psychodermatosis

Drug (class)	Action	Most common side effects	Dose	Observations
Fluvoxamine (antidepressant)	Selective serotonin reuptake inhibitor (SSRI)	Transient nausea, sexual dysfunction	50–300 mg	Arnold LM et al. J Clin Psychopharmacol. 1999;19(1):15–8. Stanley MA et al. J Clin Psychopharmacol. 1997;17(4): 278–83
Fluoxetine (antidepressant)	SSRI	Transient nausea, decreased appetite, insomnia, anxiety, sexual dysfunction	20–80 mg	Simeon D et al. J Clin Psychiat.1997; 58(8): 341–7. Christenson GA et al., Am J Psychiat. 1991; 148(11): 1566–71. Winchel RM et al. J Clin Psychiat. 1992; 53(9): 304–8. Koran LM et al. Psychopharmacol Bull. 1992; 28(2): 145–9. Streichenwein SM, Thornby JI. Am J Psychiatry. 1995; 152(8): 1192–6(Negative long-term result)
Sertraline (antidepressant)	SSRI	Transient nausea, decreased appetite, insomnia, anxiety, sexual dysfunction	50–250 mg	Dougherty DD et al. J Clin Psychiat. 2006; 67(7): 1086–92
Citalopram (antidepressant)	SSRI	Nausea, headache, sexual dysfunction	20–60 mg	Stein DJ et al. Eur Arch Psychiatry Clin Neurosci. 1997; 247(4): 234–6
Escitalopram (antidepressant)	SSRI	Nausea, headache, sexual dysfunction	10–20 mg	Keuthem NJ et al. Int Clin Psychopharmacol. 2007; 22(5): 268–74. Gadde KM et al. Int Clin Psychopharmacol, 2007; 22(1): 39–42
Clomipramine (antidepressant)	SSRI	Dry mouth, constipation, increased appetite, sexual dysfunction	25–250 mg	McGuire JF et al. J Psychiatr Res. 2014; 58: 76–83. Bloch MH et al. Biol Psychiat. 2007; 62(8): 839–46. Leonard HL et al. Arch Gen Psychiat. 1991; 48(9): 821–7. Swedo SE et al. N Engl J Med. 1989; 321(8): 497–501. Rothbart R et al. Cochrane Database Syst Rev. 2013; 11: CD007662
				Electrocardiogram before starting use is recommended, for possible cardiac conduction problems
Venlafaxine (antidepressant)	Selective serotonin and noradrenaline reuptake inhibitor	Dry mouth, constipation, nausea	37.5–225 mg.	Ninan PT et al. Psychopharmacol Bull. 1998; 34(2): 221–4
Olanzapine (neuroleptic)	Antidopaminergic	Sedation, increased appetite, sexual dysfunction	2.5–15 mg	Rothbart R et al. Cochrane Database Syst Rev. 2013; 11: CD007662. Van Ameringen M et al. J Clin Psychiat. 2010; 71(10): 1336–43. Stewart RS et al. J Clin Psychiat. 2003; 64(1): 49–52
Pimozide (neuroleptic)	Antidopaminergic	Sedation, increased appetite, sexual dysfunction	1–8 mg	Stein DJ et al. J Clin Psychiat. 1992; 53(4): 123–6
				Used to enhance the effect of SSRIs
Risperidone (neuroleptic)	Antidopaminergic	Sedation, increased appetite, sexual dysfunction	0.5–8 mg	Stein DJ et al. J Clin Psychiat. 1997; 58(3): 119–22
				Used to enhance the effect of SSRIs
Aripiprazole (neuroleptic)	Partial dopaminergic and serotonergic agonist	Sedation, increased appetite, sexual dysfunction	10–30 mg	White MP et al. J Clin Psychopharmacol. 2011; 31(4): 503–6

Other medications and therapies: there is no evidence on the use of benzodiazepines or other types of antidepressants in impulsive behavior control related to excoriation disorder. Doxepin, a tricyclic antidepressant with a potent antihistamine effect, has been used by some professionals, especially dermatologists, but there is no strong evidence in the literature to substantiate its use [67, 68]. More recently, *N*-acetylcysteine, used as mucolytic and as an antidote for acetaminophen overdose, seems to have demonstrated good reduction in symptoms when compared with placebo, especially after 12 weeks of use, in increasing dosages of 1200–3000 mg/day with mild side effects which did not lead to withdrawal of drug use, such as nausea, dry mouth, constipation, and dizziness [69, 70]. Neuromodulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), have not yet been described in cases of excoriation disorder, but as they are treatments with robust evidence for depressive and clinical anxiety settings, they deserve attention in respect of the potential therapeutic arsenal for psychodermatosis.

Psychotherapeutic

Cognitive-behavioral therapy is the psychotherapeutic approach with more evidence of efficacy, especially when behavioral techniques of habit reversal and reinforcement/acceptance are used [71–73]. Habit reversal training (HRT) comprises three basic aspects: behavioral awareness training, competitive behavior training (but healthier), and social support, especially family [74]. Reinforcement/acceptance behavioral techniques consist basically of education on behavioral condition, habit reversal techniques, acceptance techniques, and commitment (especially for avoiding situations) [75].

This combination of techniques also involves the identification of values in one's life and examination of how damaging one's own skin affects the individual's ability to move toward these values.

It also analyzes the attempts to control impulses and other negative personal experiences surrounding the phenomenon of scarring, and how these control strategies worked in the past, providing alternative behaviors and alternative feelings, exercises to undo the merge between feeling/thinking and acting (behavior of automatization), instructing the individual to live through personal emotional experiences as mere thoughts, feelings, or emotions, not as triggers of harmful behavior [73]. These techniques can be performed individually or in groups, but professionals should be well trained to be able to identify situations and correct them properly. There are no reports of family psychotherapeutic approach strategies for neurotic excoriation, but the family should be warned not to be a facilitator of such behaviors and not to allow the patient to become used to self-harm attitudes.

Final Considerations

The body has many languages, and the skin communicates emotions and organ functioning as well as internal systems in a most peculiar way. Frequent medical consultations motivated by skin issues associated with personal, family, and social psychological distress, failure of general and dermatologic medical training particularly regarding a satisfactory approach to the aforementioned issues, as well as the complexity of clinical presentations and their possible comorbidities determine a demand to re-evaluate both health education and care concerning psychodermatology.

More than specific cosmetic issues, innumerable emotional "cries for help" arising from skin manifestations demand teamwork and organized action from primary care medical doctors, dermatologists, psychiatrists, and psychologists, in the same physical setting whenever possible, providing easy access to these specialists for the patient. Valorization of doctor-patient attachment should be shown by attentive listening during a careful account of disease history, including stressor and triggering events, which should be carried out slowly before a physical examination

while encouraging the patient to elaborate his concerns and difficulties verbally, instead of showing them through skin injuries.

Usually these patients tend to deny the possibility of underlying psychological conditions and have poor self-esteem: direct confrontation and referral to a psychiatrist may reproduce a sense of latent abandonment and engender suicidal thoughts or other severe psychiatric conditions. Therefore, the inclusion of a mental health professional in the psychodermatosis patient's medical care team should be equally cautious: instead of a routine referral, where the patient – certainly coming from a great deal of medical shopping – would feel worthless or misunderstood in his complaints, issues such as difficult disease control, number of attempts at different sorts of treatment, financial cost, as well as personal investment and frustration (information obtained only by a well-conducted anamnesis) may be discussed with him or her up to the point where the logical consequence would be to consider the benefits of an association of knowledge that the inclusion of psychotherapeutic or drug treatment concomitant with dermatologic follow-up would provide.

Glossary

Anagen phase The growth phase in the hair growth cycle during which a newly formed hair continues to grow. It is generally the longest phase and is followed by catagen.

Borderline personality disorders (BPDs) *BPD* is a pattern of abnormal behavior characterized by extreme fears of abandonment, unstable relationships with other people, sense of self, or emotions, feelings of emptiness, frequent dangerous behavior, and self-harm. Symptoms may be triggered by seemingly normal events. This pattern of behavior typically begins by early adulthood, and occurs across a variety of situations. People with BPD often engage in idealization and devaluation of others, alternating between high positive regard and great disappointment. Substance abuse, depression, and eating disorders commonly coexist with borderline personality disorder. About 6% die by suicide.

Catagen phase The catagen phase is a short transition stage that occurs at the end of the anagen phase. It signals the end of the active growth of a hair. This phase lasts for about 2–3 weeks while the hair converts to a club hair. A club hair is formed during the catagen phase when the part of the hair follicle in contact with the lower portion of the hair becomes attached to the hair shaft. This process cuts the hair off from its blood supply and from the cells that produce new hair. When a club hair is completely formed, about a 2-week process, the hair follicle enters the telogen phase.

Histopathology Refers to the microscopic examination of tissue in order to study the manifestations of disease. Specifically, in clinical medicine histopathology refers to the examination of a biopsy or surgical specimen by a pathologist, after the specimen has been processed and histologic sections have been placed onto glass slides. In contrast, cytopathology examines free cells or tissue fragments.

Intermittent explosive disorder *Intermittent explosive disorder* (sometimes abbreviated as *IED*) is a behavioral disorder characterized by explosive outbursts of anger and violence, often to the point of rage, which are disproportionate to the situation at hand (e.g., impulsive screaming triggered by relatively inconsequential events). Impulsive aggression is unpremeditated, and is defined by a disproportionate reaction to any provocation, real or perceived. Some individuals have reported affective changes prior to an outburst (e.g., tension, mood changes, energy changes).

Munchausen syndrome A psychiatric factitious disorder whereby those affected feign disease, illness, or psychological trauma to draw attention, sympathy, or reassurance to themselves. Casually referred as *hospital addiction syndrome, thick chart syndrome*, or *hospital hopper syndrome*. Munchausen syndrome fits within the subclass of factitious disorder with predominantly physical signs and symptoms, but patients also have a history of recurrent hospitalization, traveling, and dramatic, extremely improbable tales of their past experiences. The condition derives its name from the fictional character Baron Munchausen.

Onychophagy Also known as *nail biting* or *onychophagia*, it is an oral compulsive habit sometimes described as a parafunctional activity, the common use of the mouth for an activity other than speaking, eating, or drinking. Onychophagy is considered an impulse control disorder in the DSM-IV-R, and is classified under obsessive–compulsive and related disorders in the DSM-5. The ICD-10 classifies it as "other specified behavioral and emotional disorders with onset usually occurring in childhood and adolescence."

Paraphilia *Paraphilia* (also known as *sexual perversion* and *sexual deviation*) is the experience of intense sexual arousal to atypical objects, situations, or individuals. No consensus has been found for any precise border between unusual sexual interests and paraphilic ones. The number and taxonomy of paraphilias is under debate. The DSM-5 has specific listings for eight paraphilic disorders. Several subclassifications of the paraphilias have been proposed, and some argue that a fully dimensional, spectrum or complaint-oriented approach would better reflect the evidence.

Prader–Willi syndrome A rare genetic disorder whereby seven genes (or some subset thereof) on chromosome 15 (q 11–13) are deleted or unexpressed (chromosome 15q partial deletion) on the paternal chromosome. It was first described in 1956 by Andrea Prader (1919–2001), Heinrich Willi (1900–1971), Alexis Labhart (1916–1994), Andrew Ziegler, and Guido Fanconi of Switzerland. Characteristic of PWS are "low muscle tone, short stature, incomplete sexual development, cognitive disabilities, behavior problems, and a chronic feeling of hunger that can lead to excessive eating and life-threatening obesity." The incidence of PWS is between 1 in 25,000 and 1 in 10,000 live births.

Psychodermatology The study of skin disorders using psychological and psychiatric techniques, a subspecialty of dermatology. Frequently treated conditions are psoriasis, eczema, hives, genital and oral herpes, acne, warts, skin allergies, pain and burning sensations, hair loss, and compulsive skin picking and hair pulling. Psychological or psychiatric treatments are the primary treatments for some dermatologic disorders, including trichotillomania and skin picking. Techniques include relaxation, meditation, hypnosis and self-hypnosis, psychotropic medications, biofeedback, and focused psychotherapy.

Schizophrenia A mental disorder characterized by abnormal social behavior and failure to understand reality. Common symptoms include false beliefs, unclear or confused thinking, hearing voices, reduced social engagement and emotional expression, and a lack of motivation. People with schizophrenia often have additional mental health problems such as anxiety disorders, major depressive illness, or substance use disorder. Symptoms typically come on gradually, begin in young adulthood, and last a long time.

Social phobia Also known as *social anxiety disorder (SAD)*, it is an anxiety disorder characterized by a significant amount of fear in one or more social situations causing considerable distress and impaired ability to function in at least some parts of daily life. These fears can be triggered by perceived or actual scrutiny from others. It is the most common anxiety disorder and one of the most common psychiatric disorders, with 12% of American adults having experienced it.

Telogen phase The telogen phase is the resting phase of the hair follicle. When the body is subjected to extreme stress, as much as 70% of hair can prematurely enter a phase of rest, called the telogen phase. This hair begins to fall out, causing a noticeable loss of hair. This condition is called telogen effluvium. The club hair is the final product of a hair follicle in the telogen stage, and is a dead, fully keratinized hair. Fifty to 100 club hairs are shed daily from a normal scalp.

Tourette's disorder Tourette's disorder (also called Tourette's syndrome, Gilles de la Tourette syndrome, GTS or, more commonly, simply Tourette's or TS) is an inherited neuropsychiatric disorder with onset in childhood, characterized by multiple physical (motor) tics and at least one vocal (phonic) tic. These tics characteristically wax and wane, can be suppressed temporarily, and are preceded by a premonitory urge. Tourette's is defined as part

of a spectrum of tic disorders, which includes provisional, transient, and persistent (chronic) tics.

Trichobezoar Trichobezoars or human hairballs are complications of trichophagia or eating of the hair. Trichophagia occurs when hair that is pulled out is chewed and then swallowed. The hair will eventually collect in a sufferer's stomach and will cause stomach problems such as indigestion and pain. Trichophagia is very commonly associated with trichotillomania.TrichomalaciaA rare genetic condition resulting in patchy hair loss in children. It is an abnormality of the hair shaft and can be due to a compulsive habit of pulling hair on the head or even eyelashes and eyebrows.

Trichotillomania Also known as *trichotillosis* or *hair pulling disorder*, trichotillomania is an obsessive–compulsive disorder characterized by the compulsive urge to pull out one's hair, leading to hair loss and balding, distress, and social or functional impairment. It may be present in infants, but the peak age of onset is 9–13 years. It may be triggered by depression or stress. Owing to social implications, the disorder is often unreported and it is difficult to accurately predict its prevalence. Common areas for hair to be pulled out are the scalp, eyelashes, eyebrows, legs, arms, hands, nose, and the pubic areas.

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Part VIII

Emerging Issues of Dermatology in Public Health

Air Pollution and the Skin Health

48

Adriano Heemann Pereira Neto, Luiza Metzdorf,
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Key Points
- The main polluting agent related to human health problems, according to the WHO, are the particulate materials
- Among the air pollution effects on human health are systemic problems (such as respiratory, cardiac, and rheumatic disorders) and skin disorders
- Early aging, atopic dermatitis, rash, acne, melasma, and skin neoplasias are related to the effects of air pollution
- Global measures and responsibilities of governmental institutions must be demanded to decrease the emission of pollutants noxious to human health

- Individual preventive measures must be stimulated to soothe the impact of air pollution on human health and skin health

Introduction

Population increase, propagation of the means of transport accompanied by the burning of fossil fuels, and pursuit of financial gain that triggers an accelerated industrialization process have all increased world pollution [1] by practically immersing the population in particulate residues in the air, garbage, soil chemical products, and waste, as well as contaminated water in the aquatic environment. According to the World Health Organization (WHO), pollution has been defined as the contamination of both the inner and outer environment by any chemical, physical, or biological agent that changes the natural characteristics of the environment [2].

"Pollution" can be classified in different ways Examples include air, land, light, noise, thermal, visual, and water pollution. In this chapter we focus on the impact of external air pollution on the skin, a type of pollution that has concrete relationships with environmental changes, quality of life, and human health [3, 4].

Environmental pollution has its origins in established sources, usually of industrial and mobile origin, such as highways and air traffic.

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The multiple types of particles and substances in such emissions are divided into primary and secondary pollutants. According to the Brazilian Environment Ministry (MMA), primary pollutants are substances directly emitted by their sources into the environment, such as particulate materials and gases, whereas secondary pollutants include substances resulting from chemical reactions, or heat reaction, as well as ultraviolet (UV) radiation from primary pollutants with substances present in the lower layer of the atmosphere, for example, ozone and peroxyacetyl nitrate [5].

The main kinds of air pollutants are highly variable depending on the referred author and the literature. According to the Brazilian MMA [5], air pollutants include aldehydes (RCHO), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), hydrocarbons (HCs), particulate matter (PM), carbon monoxide (CO), ozone (O_3), and short-life climate pollutants (PCVC). Furthermore, when the American literature is considered, according to the Environmental Protection Agency, for example, some divergences can be found, since pollutants are divided into six common types [6], so-called criteria, since they are the most common pollutants associated with changes in human health [7].

Among polluting materials, their origins, their significance for pollution, and mainly their relationship with the development of health problems are highly variable. This is important from a physician's perspective because, as will be shown here, it is not merely exposure to a polluted environment that will make an individual more prone to comorbidity, but more importantly the elements to which he or she is exposed. Thus, it is very important that the physician has knowledge of the polluting materials and, moreover, that he knows the environment in which his patients are exposed.

The main polluting agent related to human health problems, according to the WHO, is particulate matter (PM). This form of pollutant is a complex mixture of solid elements of small diameter that comprises different substances (smog, tobacco smoke, pollen, house dust mite allergens, and gaseous contaminants) of different origins, chemical compositions, and physical features [5, 6]. Such substances are divided into three major groups according to their mean diameter: ultrathin particles when their diameter is less than 0.1

μm ($PM_{0.1}$), thin particles when their diameter is less than 2.5 μm ($PM_{2.5}$), and thick particles when their mean diameter is less than 10 μm (PM_{10}).

The variation in diameter is very important for the medical practice, since the smaller the size of the particulate, the greater is its power to penetrate the respiratory tract, possibly reaching the endothelium through cell junctions and gaining access to the interstices and the vascular system, and, of course, the possibility of carrying other toxic substances, bacteria, and viruses. Furthermore, the emission source of those particles is distinct; $PM_{2.5}$ is produced more through combustion, such as in industries, automobiles, and land burning and mainly composed of nitrates, sulfates, and carbon organic compounds, whereas PM_{10} results from mechanical processes that emit bigger particles into the air, such as dust, fog, aerosol, smoke, and soot [8, 9].

The effects of PM on the human health are very diverse. In fact, these particles are the main elements responsible for pollution-related diseases, and therefore are the most commented on in the literature. They encompass systemic assaults, from mainly respiratory ones caused by increased proinflammatory factors and direct cell damage, such as asthma, pulmonary neoplasias, chronic obstructive pulmonary disease (COPD), to exacerbations of cardiac and rheumatic diseases caused by an increased inflammatory reaction, and, as discussed herein, dermatologic diseases [9]. Significant pollutants related to human health are listed in Table 48.1.

According to the WHO report, about 9 out of 10 city dwellers in the world are subject to pollution levels above the acceptable standard levels. In that 2016 report most of the citizens on the planet do not adhere to policies regarding safe levels of air pollution, leaving only 12% of the population in the investigated cities capable of breathing healthy and safe air. Worse is the fact that about half of the investigated urban population is exposed to pollution levels of less than 2.5-fold higher than the recommended levels [11]. In the United States, for example, in 2014 the Environment Protection Agency reported that more than 142 million Americans lived in areas where the air quality did not reach the environmental national standards of quality of the air,

Table 48.1 Primary and secondary compound pollutants related to human health impairment [5, 6, 10]

	What it is	Sources	Effects	Standard levels
$PM_{2.5}$	Composed of particles and organic compounds of <2.5 μm diameter	Car combustion	Respiratory tract diseases (asthma, COPD)	Must not exceed 10 μg/m³ per year, or 25 μg/m³ for 24 h
		Industries	Exacerbation of cardiovascular diseases	
		Natural burning for site clearing	Systemic inflammation	
PM_{10}	Composed of particles and organic compounds with diameter of <10 μm	Combustion processes	Respiratory diseases	Must not exceed 20 μg/m³ (annual mean) and 50 μg/m³ (24-h mean)
		Secondary aerosol		
Nitrogen dioxide (NO_2)	Heavy-smelling gas of chestnut color, highly oxidative	Volcanoes	Photochemical smog	100 ppm, up to 1-h exposure
		Bacterial actions	Acid rain	
		Electrical discharges	Combustion in thermoelectric industries, vehicles, and incinerators	
		Combustion		
Ozone (O_3)	Secondary pollutant resulting from other pollutants. It has a highly oxidative power in the troposphere. It acts in the stratosphere by absorbing solar radiation and refraining part of the UV rays from reaching the Earth's surface	Not directly emitted to the atmosphere, being produced photochemically and by solar radiation over the nitric oxides and volatile organic compounds	Asthma worsening	0.1 ppm
			Respiratory deficiency	
			Emphysemas	
			Bronchites	
			Cardiovascular	
Aldehydes (R-CHO)	Organic compound resulting from the partial oxidation of alcohols, or from photochemical reactions	Fuel burning, mainly ethanol	Mucosal itching	86.5 ppb of formaldehyde over a maximum exposure time of 30 min
		Main examples include formaldehyde and acetaldehyde	Asthmatic crises	
			Carcinogens	
			Cephalea	
Sulfur dioxide (SO_2):	Toxic and highly oxidative colorless gas; a key factor in troposphere ozone development	In nature: volcanoes	Acid rain	0–20 μg/m³
		Burning fossil fuels with sulfur in their composition	Mucosal itching	
		Electric utilities	Burns	
		Industrial processes	Worsening cardiovascular and pulmonary problems	
Methane hydrocarbons (HC)	HC found as gases, thin particles, or drops. Methane: colorless and odorless gas, highly explosive	Fossil fuel burning	Ozone development	5000 ppm
		Fuel evaporation	Greenhouse effect	
		Ruminant digestion	Asphyxia	
		Organic waste decomposition	Cardiac arrest	
		Hydroelectric reservoirs	Unconsciousness	
		Extraction of mineral fuels (mainly petroleum);	Damage to the central nervous system	

(continued)

Table 48.1 (continued)

	What it is	Sources	Effects	Standard levels
Carbon monoxide (CO)	Odorless and colorless gas from incomplete burning of carbon-containing fuel	Fuel burning (motor vehicles, fireplaces, heaters)	Headache	9 ppm: maximum levels in closed environments
			Dizziness	10–24 ppm: maximum with no problems for human health
			Weakness	1600 ppm: death after 1 h of exposure
			Nausea and vomiting	
			Quick irregular heartbeat	
			Chest pain	
			Hearing loss	
			Blurry vision	
			Disorientation	
			Death	
Lead	Heavy metal	Combustion of leaded gasoline	Metal refineries	50 µg/m³ average over an 8-h workday
			Combustion of leaded gasoline	
			Waste incinerators	
			Battery manufacture	

which represented at that time 44.37% of the nation's population [12].

In underdeveloped and developing countries the situation is even worse. In South America, the rate of urban population growth has increased 1.05% per year resulting in urbanization and, therefore, more problems related to air pollution [13]. In Brazil, air quality standards were settled by the CONAMA n° 3/1990 resolution [14], and estimates are that more than 40% of the population lives in areas where the air quality is less than the ideal one according to the WHO [15].

São Paulo, Brazil's most populated city and one of the major population aggregation areas in the world, is an example of how pollution resulting from motor vehicle emissions has become a critical factor in the development of atmospheric pollution. São Paulo is currently seen as different from all other world megacities since it is the only one with the vehicle fleet working exclusively on biofuel mixtures. Moreover, its air-quality goals are lower than those required of the main Asian and European cities [16]. According to a study presented by the Faculdade de Medicina da Universidade de São Paulo (USP), São Paulo city

has a mean $PM_{2.5}$ of 22.17 µg/m³, reaching more than 180 depending on the time of the day [17], compared with the WHO reference value for mean $PM_{2.5}$ of 10 µg/m³ per year, and of 25 µg/m³ as the 24-h mean; in other words, almost two times the rate regarded as safe [18]. These values justify what many research studies already proved: air pollution in São Paulo accounts for more deaths than the combination of car accidents, breast cancer, and AIDS [19]. The same happens in Rio de Janeiro where, according to Reuters, an institution that carries out air quality tests detected $PM_{2.5}$ values of 65 µg/m³ in some parts of the city.

However, not only people living in big cities are exposed to risks from air pollution. On the contrary, the ten worst air qualities detected in the world are located in cities where urbanization and industrialization are not actual local concerns. Located in inland Iran, China, India, and Saudi Arabia, although these cities are not areas undergoing an industrialization process, they present incredibly high pollution levels. The three cities occupying the worst position show $PM_{2.5}$ values of 170 µg/m³ (Allahabad, India), 176 µg/m³ (Gwalior, India), and 217 µg/m³ (Zabol, Iran), whose excessive pollution

results from climate changes that dry contaminated rivers, therefore elevating the pollutants into the air from coal mines or from extreme drought that produces dust suspension in the air [20].

State of the Art

Skin Damage Mechanisms Induced by Pollution

The skin is the primary interface of the human body and the outer environment, making it an organ directly exposed to environmental pollutants. Nevertheless, most studies on the damaging effects of air pollution are focused on the respiratory and cardiovascular systems. More recently, investigators have shown an increasing interest in skin changes induced by pollution, and there already exists concrete evidence of pollution impact on the health of skin. As reported by Mancebo et al., atmospheric pollution is a known danger to public health and negatively affects many organs, but our knowledge concerning pollution effects on the skin is still limited [6].

Environmental air pollution encompasses many kinds of PM. The increase of such materials in the environment resulting from industrialization and urbanization is highly associated with morbidity and mortality worldwide, and is one of the major concerns related to environmental pollution [9].

The exact mechanisms through which air pollution results in skin-damaging effects are not yet known according to the available literature, and, despite epidemiologic and clinical studies highlighting the noxious effects of pollution in human health, research studies are lacking when the topic involves skin-related effects [8].

Recent epidemiologic studies on the impact of PM on skin show that they affect development and exacerbate skin diseases. Particulate material resulting from pollution induces oxidative stress through the production of reactive oxygen species (ROS), and the secretion of proinflammatory cytokines, such as tumor necrosis factor α, interleukin (IL)-1, and IL-8. Besides, increased ROS production, such as superoxide and radical

hydroxyl by exposure to PM, increases matrix metalloproteinases (MMPs), including MMP-1, MMP-2, and MMP-9, resulting in collagen degradation. These processes lead to an increase in inflammatory skin diseases and cutaneous aging. Ultrathin particles (UTPs), including black carbon and polycyclic aromatic hydrocarbons (PAHs), produce a higher incidence of skin cancer [9].

Exogenous Substances Penetrating the Skin

Exogenous substances can cross the cutaneous barrier and reach many different organs, resulting in serious systemic consequences. Agents that penetrate the epidermis include antigens that induce potent hypersensitive late reactions, occupational exposure agents (such as cutting oils to which machine operators are exposed), pesticides (e.g., chlordane insecticide), polychlorinated biphenyls from soil, topical medicines, and cosmetics. Mathematical models that analyze multiple routes and sites of exposure are available.

Some studies show, for example, that among cultivation workers in the Netherlands, there are estimates informing that 75% of the daily dose of pyrene, a substrate of the PAHs, was absorbed through the skin. PAHs are known cancer agents and cytochrome P450 inducers. Road-paving workers are also exposed to significant amounts of PAHs.

Physiology of Skin Absorption

The outer nuclear and dead layer of the stratum corneum is the main barrier to diffusion of exogenous agents. Most penetration occurs through intercellular regions rich in lipids, and highly lipophilic molecules display the highest penetration. Penetration depends on the constant of compound intrinsic diffusion, given that small molecules are often more soluble.

Percutaneous absorption is a process of passive diffusion that follows Fick's first law of diffusion. Often the hydrated stratum corneum shows the highest penetration. Besides this very well defined route, when dermatitis and fissures are present, permeability may be partially increased in comparison with intact normal skin.

The thicker skin is often a more efficient barrier than the thinner stratum corneum, to the extent that the scrotal skin displays higher absorption rates than the body's normal epidermis.

More precise models to determine the importance of percutaneous absorption of many materials are needed, as well as better protective measures for those individuals exposed to such materials [21].

Possible Mechanisms

Modern research studies suggest that each air pollutant on its own has a toxic action specific to the skin. From a theoretical point of view, this may be due to an outside–inside effect, for example, penetration by PM and/or organic compounds connected with a skin PM. Another possibility is an inside–outside mechanism. Therefore, it is well established that PM exposure can cause systemic effects as a consequence of (i) particles which penetrate the lungs and subsequently the circulation, and, eventually, affect the skin, and/or (ii) a resulting inflammatory reaction in the lungs which can then bring about systemic inflammatory reactions that may damage the skin [8].

Vierkötter et al. detected a close association between early skin aging and exposure to soot, a mix of carbon particles covered with PAHs. PAHs are potent binders for the aryl hydrocarbon receptor (AHR), a binder-dependent transcription factor expressed by both keratinocytes and melanocytes. Experimental evidence from cultures of keratinocytes in skin exposed to Asian dust storm particles increased the AHR expression and upregulated proinflammatory mediators.

In addition, in vitro exposure of primary human keratinocytes and melanocytes to the environment containing diesel exhaust particles was recently shown to induce the expression of gene transcription with functional relevance for the development of both wrinkles and hyperpigmented spots.

The regulatory activities of the gene seem to be mediated to a greater extent by AHR activation in both types of cells (Krutmann et al., unpublished data). Moreover, AHR activation

may lead to increased production of ROS, suggesting the possibility that the topical application of antioxidants may be useful to protect the human skin against the harmful effects induced by PMs. These studies do not exclude the possibility that carbon particles on their own, i.e., lacking in PAHs, penetrate the skin, thus resulting in harmful effects as shown in lung epithelial cells [8].

Based on current evidence, there seem to be four active potential physiologic mechanisms that cause harmful skin effects: (1) free radicals, (2) inflammatory cascade and skin barrier, (3) AHRS, and (4) skin microflora.

Free Radicals Development

The ozone in the stratosphere has a protective effect by filtering UV solar radiation; in the troposphere, however, ozone has toxic effects on the skin. Ozone is a highly reactive compound that creates free radicals and depletes the antioxidants present in the epidermis.

Thiele et al. showed that exposure to increasing ozone doses resulted in a dose-dependent depletion of vitamins C and E, and development of malondialdehyde, a marker of lipid peroxidation. Moreover, ongoing low-level exposure to ozone resulted in cumulative oxidative damage to the stratum corneum. Two similar studies conducted by Thiele's group also showed that ozone depletes both the nonenzymatic and the enzymatic antioxidant stores in the skin (i.e., uric acid, vitamin C, tocopherol, glutathione), resulting in lipid peroxidation and protein oxidation, thus suggesting that pollution may induce a dysfunctional barrier [8]. There are two main mechanisms that limit these research studies. Firstly the researchers exposed mice to oxygen levels higher than the levels found in the environment and secondly, the mouse epidermis is significantly thinner than the human epidermis.

McCarthy et al. exposed normal human epidermal keratinocytes (NHEKs) to environmentally relevant ozone levels (e.g., 0.4 and 0.8 ppm) for 30 min. Results showed that exposure to 0.8 ppm of ozone leads to DNA fragmentation and ATP depletion, therefore suggesting that the mitochondrial function can also be impaired.

He et al. tested the effects of environmentally realistic levels of ozone (e.g., 0.8 ppm) in humans. The research assessed the clinical changes occurring in the human skin after short-term in vivo exposure to ozone. There was a 70% decrease in the levels of endogenous vitamin E and a concomitant 230% increase in lipid hydroperoxide in the stratum corneum. By comparison, higher doses of ozone (e.g., 5–10 ppm) were necessary to induce similar increases in the lipid peroxidation markers of mouse skin, thus suggesting that the human stratum corneum may be biochemically more sensitive to the effects of ozone [6].

Other experimental studies with mice showed not only increased levels of oxidative stress markers, but also signs of cell stress modulated by proinflammatory markers (cyclooxygenase-2), heat-shock proteins (HSP32, HSP70, HSP27), nuclear factor κB (NF-κB), and MMPs [8].

Induction of the Inflammatory Cascade and Skin Barrier Disturbances

Many studies have suggested that air pollution instigates inflammation. Cytokines and interleukins are small proteins derived from a great variety of cells involved in cell signaling and inflammatory cascade induction. IL-8 is a proinflammatory mediator of the innate immune system with two primary functions: induction of neutrophil chemotaxis and other granulocytes, and activation of phagocytes. Pollutants, such as diesel exhaust particles (DEPs), have been proved to induce a strong inflammatory reaction in human skin cells, including a significant increase of IL-8 production. Later studies gave more support to these findings by showing that exposure to DEPs in concentrations relevant to humans increases expression of NF-κB, a transitional factor that regulates the expression of proinflammatory cytokines in mouse epidermal cells.

Besides DEPs, dust particles with a complex mixture of heavy metals have been shown to increase the gene expression of proinflammatory cytokines in human epidermal cells. Choi et al. incubated NHEKs over 24 h with sterilized powder from particles derived from three Asian dust storms that happened over the time period 2004 to 2006. The epidermal cells displayed a signifi-

cant increase in mRNA expression of proinflammatory IL-6 and IL-8 cytokines, and in granulocyte and macrophage colony-stimulating factor. Furthermore, this study showed that epidermal cells significantly expressed caspase-14, a protein found in differentiated keratinocytes and involved in hydration and keratinization of the stratum corneum. The increased caspase-14 suggests that skin cells initiate a compensatory mechanism as a reaction to exposure to dust particles. As a whole, these studies suggest that air pollution induces an epidermal proinflammatory state that probably changes the epidermal differentiation and, consequently, affects the skin's immunologic barrier [6].

Activation of the Aryl Hydrocarbon Receptor

The AHR is a cytosolic transcription factor activated by binders found in many kinds of skin cells which regulate cell proliferation, inflammation, and melanogenesis. AHR activation results in translocation to the nucleus where it becomes a complex with the AHR nuclear translocator, and binds to specific sites of DNA known as a xenobiotic reaction element (XRE). Genes with XREs include the enzymes of cytochrome detoxification P450 (CYP). The AHR activation may have a role as mediator in the toxic effects associated with exposure to xenobiotics, including atmospheric pollutants, such as ozone, dioxins, and PAHs [22]. Many research studies have examined the role of the AHR activation in cutaneous mechanisms, from melanogenesis regulation to the development of skin inflammatory lesions. Tauchi et al. developed a lineage of transgenic mice that expressed the activated AHR in the absence of binder stimulation. In these mice AHR activation led to the development of a severe cutaneous eruption together with pruritus and inflammation similar to atopic dermatitis (AD). The genetic profile analysis of the mouse skin showed a significant positive regulation of genes associated with inflammatory cascade reactions. These results imply that activated AHR and AHR target genes may be involved in the development of skin adverse reactions in reaction to AHR binders [6, 8].

Besides chronic inflammation, AHR has been shown to play a primary role as a melanogenesis regulator. Luecke et al. exposed melanocytes from human donors to 10 nM 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) over 5 days, and measured the tyrosinase activity and the melanin content in vitro. After a 3-day exposure to TCDD, the tyrosinase activity was highly increased in the melanocytes, being suppressed by the concomitant treatment with oxy-4′-nitroflovane or β-naphthoflavone, partial antagonists of the AHR. After a 5-day treatment with TCDD, the melanocytes displayed an increased level of tyrosinase activity and a three-fold increase in the total content of intracellular melanin. A similar study carried out in human cells of FM55 melanoma showed that TCDD significantly increases the melanin content, thus verifying that the melanogenic route was positively regulated by AHR activation.

AHR was also identified as an ozone sensor. Afaq et al. exposed NHEKs to 0.3 ppm ozone over 20 min, and collected epidermal cells immediately after, 3 h after, and 6 h after exposure. In this study the ozone induced nuclear translocation of the AHR and increased the expression of mRNA AHR. In addition, the ozone markedly increased the expression of the isoform proteins and mRNA CYP1. CYP1 enzymes are known as compounds that metabolize compounds more toxic than the respective original compounds and activate many xenobiotic procarcinogens [6].

Skin Microflora Alterations

The resident cutaneous microflora is useful to maintain homeostasis and hinder the growth of harmful microorganisms. It was shown that environmental air pollutants change skin microflora.

He et al. showed that in vivo exposure of the human skin to ozone led to a 50% decrease of resident skin microflora, thus suggesting bactericidal effects of ozone.

Sowada et al. investigated the relationship between skin microflora and PAH metabolism. They isolated bacterial species of the human skin that can degrade benzo(a)pyrene (PaB), a PAH prototype. The species of isolated bacteria were able to use PaB as their sole source of carbon and energy. These findings raised the question of whether skin bacteria have a protective or a harmful effect on the skin regarding PAH metabolism, since total metabolism of PAH can protect the skin whereas partial degradation can result in bioactivation and increased skin toxicity [6].

Today our knowledge of the effects of atmospheric pollution on the skin remains limited. Considering the increasing trend of urbanization and increased air pollution in cities around the world, more research studies are necessary to help understand the mechanisms implied in the harmful effects of air pollutants. Prospective research studies must be designed to mimic real-life situations and examine short-term and long-term pollution effects on the skin. Moreover, these studies must deal with the methodological limitations. Lastly, owing to scarce scientific evidence, there are no established guidelines currently available for skin protection against air pollution. Besides decreased exposure, potential protective strategies must focus on rehabilitation of the skin barrier by replenishing antioxidative stores and reducing inflammation caused by air pollutants [6].

Relationship Between Pollution and Systemic Disease

Early studies that analyzed the association of the effects of atmospheric pollution with the human health date back to the twentieth century, and reported significant increases of morbidity and mortality in cities in developed countries [24].

Researchers are increasingly interested in the various effects of pollutants on human health. Recent major epidemiologic research studies identified that exposure to air pollution either in the short or long term, including exposure to PM and ozone, increases respiratory and cardiovascular morbidity. Long-term exposure was also associated with development of some forms of cancer [23].

Cardiopulmonary Morbidity

The impact caused by air pollution particles on morbidity has been a focus of ongoing studies, resulting in a solid scientific consensus on the independent association between air $PM_{2.5}$ and PM_{10} with negative impacts on respiratory and cardiovascular health,

both in the short term and in chronic exposures. Furthermore, data strongly suggest that these effects are limitless within the investigated range of environmental concentrations, possibly occurring in $PM_{2.5}$ concentrations, and also that they mostly follow a linear concentration–reaction function. Evidence is well established concerning the reduction in pulmonary function, increase in symptom severity in individuals with asthma, COPD, and ischemic heart disease including heart attacks.

More recently, evidence has linked long-term exposure to $PM_{2.5}$ to atherosclerosis, a condition underlying many cardiovascular diseases. The promotion and the vulnerability of atherosclerotic plaques represent a potential mechanism through which air pollution PM may trigger cardiovascular mortality and morbidity.

Supporting this theory, long-term exposures to $PM_{2.5}$ concentrations, as well as proximity to traffic, are associated with preclinical markers of atherosclerosis (the carotid intima-media thickness and calcification of the coronary artery) [25–28] in addition to pathology progression [27]. Gas and particle atmospheric pollutants also have a close and marked relationship with hospital admissions or mortality resulting from cerebrovascular disorders [33].

Emerging respiratory data link long-term PM exposure to respiratory diseases during childhood. Birth cohort studies have suggested an association between PM exposure during pregnancy and higher respiratory need, airway inflammation, and increased susceptibility to respiratory infections.

The most recent birth meta-analysis of the ESCAPE project also provides solid evidence that postnatal exposure to PM_{10} (but not $PM_{2.5}$) and traffic exposure are associated with an increased risk for childhood pneumonia, as well as evidence of an association with otitis media. In a birth cohort in the Netherlands other associations were reported between long-term exposure to traffic-related air pollution in the place of birth and symptoms of asthma and low-level pulmonary function during childhood [29, 30]. Another interesting epidemiologic observation notes a possible connection between chronic exposure to PM during childhood and COPD vulnerability during adulthood [29].

In regard to nitrogen dioxide, most of the research studies have found an association between NO_2 and medical appointments for respiratory diseases. The associations between PM_{10} and nitrogen dioxide on the one hand and respiratory diseases on the other hand were higher among the elderly. Air pollution possibly worsens pre-existing diseases more prone to affect the elderly population. In addition, the aging process is characterized by a decrease in antioxidant defenses, and the elderly constitute a high-risk group for oxidative phenomena induced by air pollution [29].

Long-term exposure to air pollution by thin particles related to exhaust is a significant environmental risk factor for cardiopulmonary and lung cancer mortality. Each 10-$\mu g/m^3$ elevation in atmospheric pollution by thin particles was reported to be associated with about 4%, 6%, and 8% more risk for all-cause mortality, cardiopulmonary mortality, and lung cancer mortality, respectively [31].

Some research studies hypothesize that exposure to air traffic pollution, nitrogen dioxide, $PM_{2.5}$, and PM_{10} during pregnancy and the first year of life would be associated with autism. New epidemiologic and toxicologic studies may help determine whether such a causal association exists [32].

Effects of poor-quality air on the population's health are frequently not visible in comparison with other more easily identifiable factors. Epidemiologic studies, however, have shown important correlations between exposure to atmospheric pollutants and effects of morbidity and mortality from respiratory (asthma, bronchitis, pulmonary emphysema, and lung cancer) and cardiovascular problems, even if concentrations of atmospheric pollutants do not exceed the current air quality standards. Children, the elderly, and persons with respiratory diseases are the most vulnerable populations [31].

Cutaneous Diseases Triggered and Aggravated by Pollution

The skin is the primary interface with the external environment and is, therefore, directly exposed to environmental pollution. It is thus reasonable to assume that air pollutants are also

involved with the skin disease process. Despite a few persistent doubts, researchers' interest in this topic is increasing, and there already are concrete elements that connect air pollution to dermatologic problems. A discussion of these pathologies follows.

Early Aging

Aging is a natural process that leads to the progressive loss of all tissues' structure and function. The cutaneous aging process is the most perceptible process that brings about functional, social, and psychological impacts.

Skin senescence occurs as a combination of two processes: intrinsic and extrinsic aging. Intrinsic aging is related to the long-term accumulation of cell damage by ROS of the organism itself. Extrinsic aging in its turn is associated with exposure to free radicals created by many environmental factors, such as UV radiation and cigarette smoke. Therefore, the latter process is more easily modifiable from the preventive point of view.

The extrinsic aging process is clinically, histologically, and molecularly different from the intrinsic process. Signs of extrinsic aging include coarse wrinkles, irregular pigment spots, and elastosis [34].

The external cause more associated with extrinsic aging is UV solar radiation exposure, so that for decades words like photoaging and extrinsic aging were almost synonymous. Environmental pollutants, especially PM, are also related to aging [35].

In 2010, an epidemiologic study aimed at assessing the effect of pollution exposure on the skin was published. Letters were sent to 400 women living in rural and urban German areas previously chosen, since these women were exposed to air PM from traffic and steel and coal industries. Follow-up questionnaires were distributed, followed by dermatologic assessment through the SCINEXA (score of intrinsic and extrinsic skin aging), a validated skin-aging score. It was noted that chronic exposure to PM in the air was associated with early aging signs, such as coarse wrinkles and, mainly, the development of pigment spots. An increase in soot and

traffic-driven particles in air concentration was associated with a 20% increase of pigment spots in the forehead and malar region [36]. This study was one of the first to examine the association between environmental pollution and harmful skin effects.

Experimental studies have shown probable mechanisms that associate environmental pollutants with aging. PM can increase the development of oxidative stress through ROS increase, which may speed up the cutaneous aging process by intervening in a series of skin functions, such as prevention of pathogen entry and repair of DNA damage [37, 38]. ROS also inhibits collagen synthesis by activating MMPs [39].

As discussed earlier in the Physiopathology section, exposure to PM can also contribute to the aging process through other mechanisms, such as an increase in the production of proinflammatory cytokines and damage in the repair system of DNA. These added pieces of evidence strengthen the notion of direct involvement of air PM in the cutaneous aging process.

Atopic Dermatitis

AD is a recurrent chronic inflammatory disease that often starts during childhood. It is believed that its development may be related to an environmental trigger in genetically prone individuals. Over its course, the disease usually shows remission and exacerbation periods. Loss of cutaneous barrier integrity is significant for the development of exacerbations, and these may be associated with exposure to environmental allergens. AD incidence is increasing worldwide [40], and environmental pollution has been implicated as a worsening factor in the disease [41].

A research study that assessed the relationship between traffic-driven pollutants and development of allergic diseases showed that long-term exposure to PM in the environment is linked to a greater risk for the development of atopic diseases, such as AD and allergic sensitization [42]. Moreover, it was reported that exposure to NO_2 from vehicle exhaustion was also significantly connected to eczema [42].

Symptom severity also seems to be affected. The intensity of AD symptoms, such as pruritus in children already diagnosed with AD, is higher when high levels of environmental PM_{10}, $PM_{2.5}$, and ultrafine particles (UFP) are detected [43].

The function of the epidermal barrier is fundamental to preventing AD exacerbations. A study assessing the loss of transepidermal water as a parameter of cutaneous barrier integrity showed that short exposure to NO_2, a UFP compound, resulted in damage to the epidermal barrier and exacerbation of AD symptoms [44].

Based on these bibliographic data, we can conclude that exposure to PM is a risk factor for AD development, as well as for exacerbations in children with a previous diagnosis of AD.

Individuals with sensitive skin are also a high-risk population facing the effects of air pollution [8]. It is more a syndrome than necessarily a disease, the concept of which is highly stressed in the specific literature, and its definition deserves some attention in the context of early subjective complaints of discomfort (burning, pruritus, stinging, xerosis, erythema, papules, or scaling) with no immunologic reaction. It is defined as a multifactorial inflammatory syndrome with signs of cutaneous hyperreactivity, while not immune to usually well-tolerated stimuli [45].

It also seems to be associated with the loss of cutaneous barrier integrity and increased permeability of the stratum corneum. Thus, external factors, including environmental pollution, have been associated with complaints by individuals with sensitive skin [45].

Urticaria

Urticaria is an impairment mediated by cutaneous mastocyte degranulation on the surface dermis that affects about 20% of the population. It may be followed by angioedema, a deeper cutaneous edema involving the dermis and the hypodermis. It is clinically characterized by an erythematous and pruriginous plaque. A single reason for the development of urticaria may be found in some patients, mainly those with a recent onset of the presentation. Many cases, nevertheless, do not have an identifiable trigger, a situation more common in cases persisting for weeks or months. The most frequently identified triggers include infections, drugs, food, and insect bites [46].

Although environmental factors can also trigger urticaria, few studies have associated environmental pollutants with its development.

A Canadian research study established a correlation between increased number of visitors to the emergency department because of urticaria with a worsening of the air quality index that used the levels of three known environmental pollutants as parameters: ozone, nitrogen dioxide, and $PM_{2.5}$ [47]. Another Chinese study showed that increased ozone levels led to a statistically significant increase of urticaria (3.84%) and other allergic diseases [48].

Acne

Acne vulgaris is a chronic inflammatory dermatologic disease originating in the pilosebaceous apparatus that leads to clinical changes in the skin, such as open and closed comedones, papules, pustules, and nodules. It has a multifactorial origin, with hormonal, hereditary, and environmental influences.

There is evidence that acne vulgaris can be worsened by increased levels of ROS and IL-8 induced by BaP exposure found in high concentrations in cigarette smoke [49]. BaP is a PAH formed by incomplete combustion of organic matter, present as an air pollutant disseminated through the air, soil, water, and sediments [50, 51]. Therefore, it can be inferred that air pollution can also play a role in acne worsening.

There is, however, one known acne variation closely connected with exposure to environmental pollutants, namely chloracne. Chloracne occurs after the systemic absorption of halogenated aromatic hydrocarbons, and is regarded as one of the most sensitive indicators of intoxication by these compounds. These agents are often called chloracnegens [52].

Chloracne is, thus, more the result of a systemic intoxication than direct contact with the skin. In other words, it is not usually associated with exposure to air pollution. Mostly it results from occupational and non-occupational exposure, the latter being associated with contact with industrial garbage and contaminated food [52].

Table 48.2 Differing characteristics between acne vulgaris and chloracne

	Acne vulgaris	Chloracne
Age group affected	Adolescence and early adulthood	Any age group
Anatomic localization	Face including the nose, upper back, chest	Retroauricular and malar areas, axillae, groin, extremities; nose is spared
Inflammation	Inflammatory lesions are common	Inflammation is very rare (only as a secondary effect after a cyst rupture)
Sebum production	Increased	Decreased; xerosis as a common associated condition
Initial lesion	Limited comedones, papules, pustules, cysts	Myriad comedones
Sebaceous gland	Hypertrophic	Atrophic; gradual replacement with keratinocytes
Sweat gland	Uninvolved	Palmoplantar hyperkeratotic lesions; acrosyringial plugging

Adapted from Panteleyev and Bickers [53]

Dioxins belong to a family of halogenated aromatic hydrocarbons, and are considered the most potent chloracne inducers. They are classified as class 1 carcinogenic [21, 22].

Chloracne is characterized by an acneiform eruption comprising comedones (blackheads and whiteheads), pustules, and cysts. Table 48.2 highlights the main differences between chloracne and acne vulgaris.

The only effective way to prevent chloracne is by avoiding exposure to chloracnegens. The treatment involves moving patients out of contaminated places and allowing the organism itself to eliminate the agent. A synthetic fat substitute, olestra, seems to accelerate the fecal elimination of chloracnegens [54].

Melasma

Melasma is an acquired disorder of multifactorial origin displaying hyperpigmentation on photoexposed areas, mainly the face. It is more common in phototype III and IV women, and causes major aesthetic harm and psychological stress that result in a negative impact on the quality of life [55].

The physiopathology of melasma is not totally understood, although many factors play a role, such as genetic predisposition, UV radiation, hormonal factors (e.g., use of contraceptives and pregnancy), thyroid dysfunction, and use of cosmetics, phototoxic drugs, and anticonvulsants [56–58].

It was recently postulated that environmental pollution might also be a contributing factor in melasma [59]. The author argues that melasma has a higher incidence in Indian and South-East Asian individuals, locations with heavier pollution [60, 61]. By referring to research studies suggesting an association of melasma with factors already linked to pollution, such as extrinsic aging [62], and inflammation [63], the author proposes that air pollution might play a synergistic role with other risk factors for melasma development. Although seeming a plausible hypothesis, there is no evidence as yet that directly correlates melasma with air pollution.

Skin Cancer

Skin cancers are the most common cancer type in the human species. About 40–50% of North Americans up to the age of 65 years will suffer from a basal cellular carcinoma or a spinal cellular carcinoma [64]. Although seen less often, melanoma is the skin cancer displaying the highest potential for fatality, and its incidence is significantly increasing [65].

Air pollution is already acknowledged as an element associated with cancer development. Traditionally lung cancer is the cancer most often associated with air pollution [66], but there are epidemiologic studies showing an association between PM and skin cancers.

In a study conducted among longshoremen in Italy, their occupational exposure to black carbon was investigated and showed an increased incidence of bladder cancer, pleural mesothelioma, and melanoma [67].

Black carbon is classified as a class 1 carcinogen, being a UFP type resulting from diesel exhaustion, so that exposure to it may occur in ways other than the occupational environment. Oddly, an association with other types of skin cancer besides melanoma was not shown [67].

Another epidemiologic study investigated PAHs, also with carcinogen potential, in the occupational environment, and found an association with lung, skin, and bladder cancers [68]. PAHs occur as mixtures within the PM derived from cigarette smoke, coal tar, and diesel exhaust [69]. PAHs may exist in the environment during their particulate and gaseous phases. The gaseous phase is more abundant although it is less carcinogenic than the particulate phase. The particulate-phase PAHs may occur as $PM_{2.5}$ and UFP [9]. PAHs can be absorbed by the skin, and their combination with carcinogenesis takes place through interaction with a specific receptor, the aryl hydrocarbon receptor (AhR) [70].

There are other studies showing the existence of a synergistic effect among environmental pollutants, such as BaP and UVA radiation, in carcinogenesis. If combined, these two agents promote cancer induction in smaller exposure doses than in separate agents [71].

Compounds such as black carbon, PAH, and BaP, are carcinogens present in the environment as compounds of air PM resulting from different human activities, and representing a risk for the whole population beyond the occupational environment. Experimental models have shown that these pollutants induce cellular changes involved with carcinogenesis with consequent skin cancer.

Approach to Pollution-Induced Skin Damage and Preventive Measures

Since it is a recent topic in the literature, there are no established guidelines with recommendations to protect the skin from pollution.

There are, nevertheless, some general measures that can be recommended by dermatologists for skin protection against damage induced by environmental pollutants [9].

- Emollients may be used to preserve and restore the cutaneous barrier, resulting in decreased penetration of pollutants into the skin.
- Daily use of gels and cleaning products may help decrease the particle load of the skin.
- Use of sunscreens may be beneficial against pollution, since there is evidence connecting the synergistic effect of UV radiation with environmental pollutants in carcinogenesis.
- Development of skin barriers with products such as BB foundations and creams may be useful as protection against pollutants, acting as oxidative damage agents through direct contact with the skin.
- Avoidance of excessive skin washing, which may be harmful to the natural cutaneous barrier, is recommended.
- Whenever possible, exposure to environments with high concentrations of pollutants should be avoided.

Experimental studies show that air pollutants, such as ozone, induce skin oxidative damage and deplete its natural antioxidants, such as vitamins C and E [72, 73]. There is also evidence that such effects may be attenuated by the topical application of antioxidants [74]. Therefore, the use of oral or topic antioxidants is an additional strategy to fight cutaneous damage induced by these pollutants.

In closed environments, strategies to control the effects of air pollution on the skin may result in a collective impact. After implementing a program of air quality improvement in nine randomly selected kindergarten in South Korea, the decreased concentrations of indoor PM_{10} brought about a significant reduction in AD symptoms. The eczema area and severity index (EASI) score was significantly decreased from 2.37 to 1.19, and the mean body surface area decreased from 7.06% to 4.22% after the program's implementation [75].

Fig. 48.1 Deaths per capita attributable to PAH in 2012, by region [2]
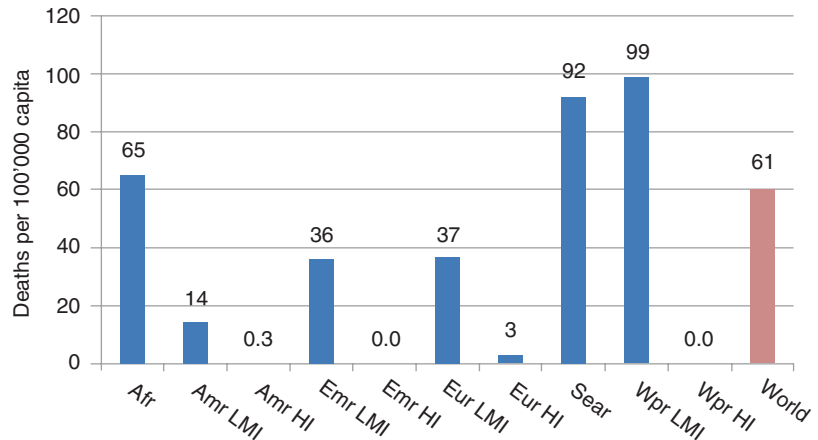
Future Perspectives

Recent vehicle-controlled clinical studies showed that a new antagonist cosmetic competitive with the AhR was effective in preventing its activation in the human skin [76]. Thus, it may be useful as a promising strategy to prevent skin damage associated with PAHs occurring through a connection to the AhRs expressed in keratinocytes and melanocytes.

A large portion of the research studies that associate environmental pollutants with skin diseases are conducted in occupational environments; therefore, more research studies are necessary at the population level so that we can obtain a more realistic idea of the environmental impact, since in the aforementioned situations exposure can be less intense and pollutants may be in lower concentrations.

Environmental pollution is a public health problem, and its effective management necessarily occurs through a decrease in pollutant exhaust. A concerted effort of companies and governments to implement effective environmental policies that positively affect public health is necessary.

To conclude this chapter, the importance of air pollution related to two indexes is illustrated: deaths attributable by region and by disease (Figs. 48.1 and 48.2, respectively), according to the WHO [2].
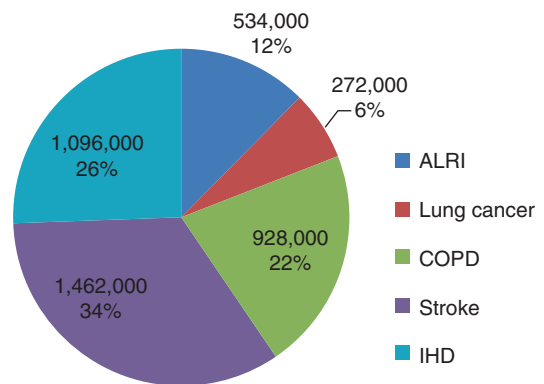
Fig. 48.2 Deaths attributable to PAH in 2012, by disease [2]

Glossary

Aging Natural process that leads to progressive loss of structure and function of all tissues.

Black carbon Environmental pollutant rated ultrafine particulate from diesel exhausts. It is a carcinogen class 1. It is associated with some types of cancer, for example bladder cancer, pleural mesothelioma, and malignant melanoma.

Chloracne Acne variant associated with exposure to environmental pollutants that develops after systemic poisoning by halogenated aromatic hydrocarbons. It is characterized by an acneiform eruption consisting of comedones (blackheads and whiteheads), pustules, and cysts.

Extrinsic aging Process associated with exposure to free radicals created by numerous environmental factors such as ultraviolet radiation and cigarette smoke. Signs of extrinsic aging are thick wrinkles, irregular pigmentation spots, and elastosis.

Intrinsic aging Process related to the accumulation over time of cell damage by reactive oxygen species from the organism itself.

Sensitive skin Inflammatory multifactorial syndrome with cutaneous hyperreactivity signals not immune to stimuli generally well tolerated, clinically characterized by subjective complaints of discomfort (burning, itching, xerosis, erythema, papules).

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Photoprotection and the Environment

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Key Points

- Photoprotection is the primary preventive and therapeutic strategy against sunburn, photoaging, and skin cancer
- Photoprotective resources include broad-spectrum sunscreens, clothing, accessories, an appropriate diet, and the choice of times of lower solar radiation
- The UV index (ultraviolet index) forecast serves to warn of the dangers of excessive sun exposure and the importance of adequate sunscreen application
- Permanent educational measures on photoprotection are required to advise health professionals and the general population from childhood onward

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Introduction

Electromagnetic Spectrum

The sunlight that falls on the skin can be absorbed, reflected, or scattered. The electromagnetic spectrum is extremely broad. Medically important wavelength ranges, however, are ultraviolet (UV) rays, visible light, and infrared (IR) radiation [1–5].

Ultraviolet Rays

UV rays have wavelengths of 100–400 nm and are divided into three bands: A (UVA), B (UVB), and C (UVC) (Fig. 49.1).

UVA radiation is subdivided into low UVA (320–340 nm), responsible for the vast majority of physiological effects on the skin, and high UVA (340–400 nm), which causes changes in the dermal structures. UVA has a direct action on the vessels of the dermis, causing vasodilation and gradual erythema. In epidermal cells, it elicits the breakdown of DNA chains that are subsequently repaired by enzymatic mechanisms. Depending on the thickness of the skin and duration of solar exposure, UVA can cause immediate and delayed pigmentation; skin aging; carcinogenesis; and the development of diseases such as lupus erythematosus, polymorphous light eruption, and photoallergies [3, 4, 6].

UVB has a wavelength range of 290–320 nm and is absorbed by ordinary glass. Despite its

reduced skin penetration, the high energy of UVB is responsible for immediate sun damage and much of the delayed sun damage. UVB causes injury to epithelial cells and induces the formation of vasodilator substances such as prostaglandins. It also takes part in epidermal vitamin D metabolism, although it may cause erythema, burns, delayed pigmentation, epidermal thickening, photoaging, and carcinogenesis [1, 7, 8].

UVC has a wavelength range of 100–290 nm. It is absorbed by the upper layers of the Earth's atmosphere that are rich in ozone. UVC hardly reaches the Earth's surface at all. Recent studies indicate the depletion of the ozone layer. Although the consequences of this are still not fully clear, it is already affecting our lives and the planet [4, 5].

Visible Light

Visible light has a wavelength range between 400 and 780 nm and enables the formation of images by stimulating the retina and helping the brain distinguish between different colors (violet, blue, green, yellow, orange, and red). It may favor the onset of eye and skin diseases [6].

Infrared Radiation

IR radiation corresponds to about 50% of the solar spectrum. It has lower frequencies and generates little power. Because it transports heat from the sun to the Earth, it is called the "caloric rays band." IR radiation reaches the hypodermis and causes temperature increases, heat, and cutaneous vasodilation. Chronic exposure to heat can lead to the development of erythema ab igne. IR radiation may contribute to pigmentation when combined with visible light [6]. It also contributes to skin aging and carcinogenesis, owing to its additive effects on UV radiation [2, 9].

In addition to the potential for interaction between the different radiation types and wavelength ranges, several environmental factors may influence the intensity of solar radiation that reaches the Earth's surface and the unprotected skin [4].

Personal characteristics, sociocultural aspects, exposure behavior and solar protection, genetic aspects related to skin pigmentation, photosensitive diseases, and immune competence are conditions that affect the health of skin [1].

Radiation Influences on the Environment

The surface levels of UV radiation depend on numerous aspects such as geography (latitude and altitude), weather (ozone levels), time (time of day and season), and sites (weather conditions, environmental pollutants, height, and cloud coverage) [5].

Latitude and Altitude

The intensity of UV rays increases with the increasing altitude of the location. This is because the atmosphere is thinner above it. However, this increase depends on other factors such as the amount of ozone in the lower layers of the atmosphere and the type of surface that reflects the rays and the sun's position [2].

Ozone

Ozone is the main absorber of UV radiation. Its highest concentration (about 80–90%) is located in the layer between 15 and 30 km altitude. This layer is responsible for the intensive absorption of UVB radiation and part of the extinction of UVC radiation [1].

Because of the existing transport mechanisms in the upper atmosphere, much of the ozone produced is transported to higher latitudes. Thus, there are lower ozone levels in the equatorial region of the planet in contrast to the pole and in regions of higher latitudes. Previous research has indicated that a decrease in ozone levels causes an increase in the risk of skin cancer development [4].

Time of Day and Season

UVB radiation is most intense between 10 a.m. and 4 p.m., with peaks recorded near midday. During the summer months, in areas closer to the equator, they increase about 4% every 300 m and can reach us from more than one direction, depending on the reflective surface area [2].

Sites

The intensity of sun radiation varies depending on the surface that it reaches. Snow, ice, white sand, grass, water, glass, and metal reflect radiation. Thus, the intensity of solar radiation striking these objects can be high even in shaded areas. Sand and concrete reflect 17% of UVB radiation while snow reflects 80% of UVB radiation. Pollutants and haze decrease the intensity of radiation, whereas clouds absorb 10–80% of UV radiation and therefore may pose a risk of overexposure [1, 6, 8].

State of Art

Influence of Sun Radiation on the Organism

Primarily due to its psychological and biological effects upon humans, natural light has been linked to positive events, such as lower rates of absenteeism and errors at work, and increased productivity levels. Its psychological effects are considered to be positive attitudes, as well as reduced fatigue and depression in patients with affective disorders. Its biological effects include the production of hormones, body self-regulation, wakefulness, and the sleep cycle [1].

When combined with physical activity, as well as with a proper diet or vitamin supplementation, natural light activates the metabolism of vitamin D [10]. This occurs when the individual receives UVB radiation. Vitamin D regulates bone and mineral physiology, especially the physiology of calcium metabolism, and in addition to having an antioncogenic role, it is also responsible for blood pressure control, the synthesis of natural antibiotics by defense cells, the modulation of autoimmunity, and the synthesis of inflammatory interleukins [11].

The endogenous production of vitamin D is influenced by melanin, and its synthesis begins in the deep layers of the epidermis, where its photochemical precursor 7-dehydrocholesterol is stored [10, 11]. Studies have shown that, regardless of age, ethnicity, geographic location, and sunscreen application, a significant portion of the world's population has low levels of vitamin D [4].

Persons predisposed to possible vitamin D deficiency may require adjustments in diet and oral supplementation with clinical monitoring [6, 7].

The Influence of Sun Radiation on the Skin

Throughout life the human skin, especially the face and back of the hands, is exposed in many ways to the action of UV, visible, and infrared

light that can cause acute health problems or chronic health. Solar radiation has significant deleterious effects on the eyes and is the main skin carcinogen [4].

Cumulative sun exposure leads to integumentary system disorders, depending on personal, racial, behavioral, and immunogenetic characteristics. Certain individuals also have a higher risk of sunburn, pigmentation, photoaging, skin injuries, and carcinogenesis than others [6]. Light-skinned people particularly react more intensely to lower doses of UV radiation than dark-skinned people. Pigment sensitivity to UV light indicates ethnic origin and was classified according to phototypes by Fitzpatrick [12] (Table 49.1).

Influence of Sun Radiation on Outdoor Activities

Sports and Recreational Activities
Outdoor physical activities expose not only participants but also the public, organizers, trainers, and the coaching staff to acute and chronic skin changes. The face, the neck, the upper chest area (the "V-neckline" area), and the backs of the hands and arms are usually the most vulnerable sites and are more directly exposed to the environment [1].

The type of sport in which a person participates and the duration of outdoor activities are risk factors for increased exposure to sun radiation. For example, street joggers are exposed to solar radiation at different times of day, which

makes them more vulnerable to the harmful effects of excessive radiation [8, 12]. Physical education teachers who work outdoors are also subject to these effects [13].

Skin lesions must be recognized, treated, and prevented to avoid compromising the participation and performance of athletes in training and competitions [8]. Drug eruptions and dermatoses, such as labial herpes simplex, erythema multiforme, and pemphigus erythematosus, can be activated by sun exposure [4, 12]. The risk of UV radiation-related health effects on the eye and immune system is independent of skin type. Some studies have demonstrated that athletes who stay longer in the sun, such as marathon runners, cyclists, and triathletes, are at greater risk of developing skin cancer [8, 12]. Other athletes who are constantly exposed to sun radiation are surfers, swimmers, boaters, and skiers, as are adventure sports, eco-tourism, mountaineering, and paragliding enthusiasts.

UV radiation exposure tends to be increased on weekends and holidays. Tourists should be informed of UV radiation levels and be encouraged to protect themselves from the sun.

Children and the most vulnerable population groups, who are particularly sensitive to UV radiation, require special protection.

Outdoor Occupational Activities
Professionals such as farmers, gardeners, postmen, public cleaning and street lighting workers, military personnel, lifeguards, sailors, fishermen, and informal trade workers, among others who

Table 49.1 Skin types and response to sun exposure (Fitzpatrick classification) [12]

	I	II	III	IV	V	VI
Skin color	Pale white	White	Cream white to light brown	Moderate brown	Dark brown	Black
Main ethnic representatives	Albinos and redheads	Blondes	Whites	Brunettes and Latinos	Arabs, Mediterraneans, mestizos, Asians Indians	Blacks African people
Response to sun exposure	Always burns, never tans	Always burns, tans minimally	Burns and tans moderately	Burns minimally, always tans well	Rarely burns, always tans well	Never burns, always tans well
Pigment sensitivity to UV radiation	Very sensitive	Very sensitive	Sensitive	Mildly sensitive	Very mildly sensitive	Less sensitive

perform outdoor occupational activities, are continuously and customarily exposed to the sun [4, 5, 14]. Although studies have already demonstrated the relationship between chronic exposure to sunlight and damage to skin health, eyes, and lips, there are still unknown pathologic mechanisms [15]. Nevertheless, the use of protective clothing and measures such as limiting the duration of sun exposure, among others, are preventive, as are therapeutic strategies implemented against the harmful and cumulative effects of radiation on adults who predominantly work outdoors [1, 8, 12]. Health education aims achieve a change in attitudes and behavior [5].

Photoprotective Measures

Effective sun protection is achieved with the use of a set of measures to reduce or mitigate exposure to sun radiation. Photoeducation, as well as the use of sunscreens, clothing, accessories, and shadows, are resources that need to be combined to achieve more effective results [1, 16–21].

Topical Photoprotection

Sunscreens are elements with prophylactic and therapeutic purpose. Its regulation varies between different regions of the world, especially in Europe, the United States, and Australia [22–24].

In Brazil a combination of various physical and chemical filters is used in products to protect against UVA and UVB radiation: namely, SPF (sun protection factor) of 30 or more and UVA protection under international recommendation [4, 6].

Sunscreens should provide broad-spectrum protection, have low cost and good cosmetic acceptance, and be stable, nontoxic, nonirritating, nonsensitizing, easy to use, and water resistant [1, 6, 24]. The active ingredients of sunscreens act through mechanisms that absorb (organic), reflect, or block (inorganic) UV light, according to their chemical nature and physical properties [2].

There is a tendency to add antioxidant factors, DNA repair enzymes, and new compounds

to increase the protective efficacy and also mitigate the effects of IR radiation [2, 9, 25, 26]. Research and development of new molecules and technological solutions for photoprotection continues [27].

The sunscreen vehicle should be compatible with the user's specific skin type and with the site of sunscreen application. Shampoos, conditioners, hair sprays, and solutions are indicated for the hair and hairy areas. Creams, lotions, and fluids are particularly suitable for dry skins. Gels are recommended for oily skin, and lipsticks for the mucous membranes. Emulsions and makeups have good cosmetic acceptability and effectiveness [2, 6, 24].

Improper use of sunscreen, however, can create a false feeling of protection. The main problems found are reduced or nonuniform sunscreen application, excessive sunscreen use to prolong the duration of sun exposure, low use of sunscreen, and faulty sunscreen reapplication [6, 20, 28].

In many outdoor work situations, as well as in situations of high sweat secretion, friction, water immersion, and repeated sun exposure, sunscreen has to be applied onto exposed areas every 2–3 h, sometimes even immediately after the first application of the product [1, 4, 13, 15]. Awareness of the dangers of excessive sun exposure should be converted to continuing protection practices and measures.

Photoprotection by Clothing and Accessories

Clothing is simple and practical, and relevant to photoprotection from childhood on [5, 6, 14, 18, 29–31]. Clothing with a sun protection function are subject to international standards and standardized with the term UPF (ultraviolet protection factor) as the category UPF 40–50 (excellent), UPF 25–39 (very good), and UPF 15–24 (good) [4, 32].

Some cotton and viscose fabrics available on the market offer protection against UV radiation. Their protection power, however, decreases as the fabric "ages" after repeated use and washings. Sun protection capacity can be increased according to the design and color of clothing, the fabric weave, the thickness of the threads, additives, and washing conditions [2, 4].

Exposure to sun radiation can be minimized by wearing socks, closed shoes, and accessories such as gloves, helmets, caps, and wide-brim (>7.5 cm) hats. Good-quality sunglasses protect the periorbital region. Clear lenses filter UVB radiation, while dark lenses filter UVA and visible light [6, 30]. The skin coverage provided by clothing and accessories works as a protective barrier against the sun. Moreover, they are easy to use, can be reused, and their cost is diluted over time.

The safety of workers and athletes during outdoor activities can be increased with the use of appropriate clothing and sportswear during work and sports. Increasingly sophisticated, resistant, practical, and easy to maintain products are manufactured to improve performance while protecting the athlete's physical integrity and health [4, 5, 8].

Systemic Photoprotection

More recently, studies have investigated the action of dietary or pharmacologic oral agents and their ability to inhibit or reverse sun damage to healthy or changed skin [6, 26, 33]. Some of the substances studied are β-carotene, green tea, isoflavones, polypodium leucotomos, lycopene, milk thistle, indomethacin, vitamin E, and vitamin C. These agents act by different or synergic mechanisms, and are available in food [34, 35]. Each case must be assessed individually, and caution is advised when prescribing these substances [4, 6, 26, 27].

Photoprotection by Behavioral Strategies

The following strategies should be prioritized as photoprotection behaviors:

Time and Place of Activities

Indoor workers receive 10–20% of outdoor workers' yearly UV exposure [5]. Outdoor activities should be scheduled in the early morning hours or preferably late afternoon, when the incidence of radiation begins to decline [1, 12], causing less damage and injuries.

The place, time of year and day, as well as seasonal and annual climate changes influence the intensity of sun radiation. Sun rays are reflected, dispersed, and absorbed many times on their way to the ground depending on the earth's rotation, tilt, and elliptical orbit around the sun. The intensity of sun rays can also vary depending on the effects caused by the formation of clouds, smog, dust, and mist [2]. The sum of these multiple components results in the overall incidence of solar radiation on a body located on the soil.

On cloudy days with little sunlight, a high percentage of UV rays comes through the clouds, increasing the risk of burns to unprotected body areas [2, 8, 16, 17]. Persons should be encouraged to reduce the occurrence of sunburn and cumulative UV radiation exposure over a lifetime [5].

UV Index

The intensity of UV radiation is wide and variable around the globe. The World Health Organization (WHO) has standardized UV measurement worldwide with the Ultraviolet Index (UV index). This index ranges from 0 to 12 or more in areas of medium altitudes, and is published daily by local meteorological bulletins. The sun protection measures should be triggered with a UV index ≥3. Extra protection is needed with a UV index of ≥7 [4, 5] (Table 49.2).

Shadow Rule

Solar radiation is less damaging the smaller the shadow of persons in relation to their height. Therefore, the larger the size of the lower body shadow, the greater the risk of radiation. This rule is an important and viable resource to identify periods of the day with less solar radiation [32].

Australia and other developed countries invest in intelligent and sustainable ecological solutions in consideration of shade in urban planning. Shade can reduce UV by 50% or more [5]. It is important to promote the modification of public places and educate the population.

Table 49.2   The World Health Organization global solar UV index (UVI)

	UV index				
	0–2	3–5	6–7	8–10	11+
Description	No danger to the average person	Little risk of harm from unprotected sun exposure	High risk of harm from unprotected sun exposure	Very high risk of harm from unprotected sun exposure	Extreme risk of harm from unprotected sun exposure
Recommended protection	Wearing a hat and/or sunglasses is sufficient	Wear a hat and sunglasses. Use SPF 15+ sunscreen	Wear a hat and sunglasses. Use SPF 30+ sunscreen. Cover the body with clothing. Avoid the sun if possible	Wear a hat and sunglasses. Use SPF 30+ sunscreen. Cover the body with clothing. Avoid the sun if possible	Take all precautions possible. It is advised to stay indoors
Sunburn time	1 h+	40 min	30 min	20 min	Less than 15 min

School and all outdoor recreational sites (beaches, sports centers and swimming pools, parks and zoos) provide information about UV radiation levels and sun protection.

The population should be encouraged to use umbrellas, tents, and other coverings especially in the summer months [5].

Eating Habits

A varied diet containing colorful (orange, yellow, and green) and natural food ingredients should be encouraged. Vitamin E, vitamin C, β-carotene, and lycopene are contained in fruits and vegetables and reduce the oxidative effects of UV radiation [33–35]. The intake of minerals (zinc, selenium, iron) and flavonoids and phenolic compounds found in grape, apple, citrus fruits, broccoli, cucumber, soybean, green tea, caffeine, and fish oil also contribute to daily photoprotection because of their antioxidant, anti-inflammatory, and immunomodulatory properties [2, 6, 27, 34].

Self-examination of the Skin

People should be encouraged to regularly check their entire skin surface for changes, including the scalp, armpits, buttocks, genitals, and feet. Self-examination of the skin surface is essential in prevention because it helps in the early detection of injuries [1]. Patients should seek medical advice if they notice any changes in their skin, or itching or bleeding injuries that do not seem to heal.

Individuals with light-colored skin and eyes, patients with multiple atypical nevi and a personal or family medical history of skin cancer, as well as outdoor athletes and workers are groups who need continuous prevention through extensive sun protection practices, health education, and early diagnosis [4, 20].

Educational Approaches for the Population

The prevention of skin cancer and other sun damage requires the implementation of permanent educational measures and awareness programs to prevent excessive and unprotected exposure to the undesirable effects of radiation [1, 4]. Children and adolescents should be afforded special attention because 50–80% of the estimated individual lifetime sun exposure occurs before 20 years of age. This refers to exposure to radiation resulting from casual exposure to sunlight in cars and other day-to-day routines, or intentional exposure during outdoor recreational and sports activities [6, 29, 31, 32]. Thus, the active participation of the family, schools, communities, businesses, government organizations, and different media is required to

disseminate qualified information about the importance of health promotion and the available photoprotective methods.

With regard to sports fans, the characteristics and types of physical activities has changed in recent years, with a special increase in devotion to jogging, sports weekends, and adventure sports [1, 8]. Furthermore, the number of participants in these sports from special populations, such as pregnant women, older people, and disabled athletes, has increased. Both professional physical activities and activities performed to improve the quality of life entail the need for more effective sun protection, which is a cross-cultural challenge [5].

Outdoor workers may be more vulnerable to sun damage because of the amount of radiation accumulated by them over time, as well as episodes of high-intensity exposure [14–16]. Preventive strategies must be contextualized, improved, and constantly updated (Table 49.3).

New sun-protection strategies continue to be developed as several promising substances and products are discovered. However, further studies are still needed in this area. The use of sunscreens, combined with the implementation of a set of photoprotective measures, including photoeducation, is fundamental to achieving effective and lasting results.

Table 49.3 Forms of protection against UV radiation

Photoprotection attitudes	General considerations about the available resources
Healthy interaction with the environment	Observe latitude, altitude, season, reflection and scattering of rays by different surfaces
	Try to stay in the shade of an umbrella, trees, or other shelter
	Avoid sun exposure between 10 a.m. and 3 p.m. (10 a.m. and 4 p.m. in daylight-saving time)
	Be especially careful on cloudy days, because even then
	80–90% of the sun's radiation comes through the clouds
	Pay attention to the UV index of your city
Clothing and accessories	Wear a cap or a hat with an 8 cm wide brim
	Wear sunglasses with good optical quality as well as UVA and UVB lenses for visual comfort
	Wearing gloves protects your hands. The use of gloves should be encouraged, especially during performance of outdoor occupational or sports activities
	Choose fabrics that transmit less UV radiation. Transmission varies according to the texture, color, type, stiffness, and moisture of the fabric
	Avoid wearing wet T-shirts outdoors in the strong sun
Balanced diet	Daily consume colorful (red, orange, and yellow), natural foods rich in β-carotene and lycopene
	Incorporate cucumber, broccoli, and other fruits and vegetables that are sources of polyphenols into your diet, as they help reduce oxidative damage
	Eat natural foods rich in minerals (zinc, selenium, iron) and vitamins E, C, and D
Sunscreens	Confer due value to safety, efficacy, quality, benefits, and cost
	Preferably use products that are specific to your skin type and provide broad UVA and UVB protection
	Choose water- and sweat-resistant sunscreens with SPF 30 or more, and UVB and UVA protection, that do not run into the eyes
	Use sunscreen daily. Apply a generous amount of sunscreen homogeneously onto the skin and make frequent reapplications during the day
	Apply sunscreen liberally and frequently to your face, ears, neck, shoulders, and hands
Permanent education and health promotion	Prevention is the best measure to reduce risks
	Always combine several protection measures
	Perform skin self-examination frequently
	Control sun exposure and see a dermatologist to receive updated information on specific guidelines to follow according to your lifestyle

Future Perspectives

Stratospheric ozone layer depletion, climate changes, increased pollution, and lifestyle changes are factors that expose the individual to sunlight. Unprotected skin exposure to UV radiation can cause burns, photoaging, and skin cancer, in addition to other damage. Studies alert to the need of using appropriate clothing, accessories, and sunscreens for broad-spectrum protection [1–5].

The UV Index, available at public locations of several cities around the world or accessed via mobile electronic devices, has been disseminated as a real-time resource for stimulating photoprotective measures and adequate sunscreen application.

Nevertheless, there are still many controversies with respect to the presence and/or toxicity of certain chemicals used in sunscreen preparations, as well as to whether rigorous photoprotection affects vitamin D3 absorption [4, 7, 10]. There are also concerns and discussions regarding health damage associated with visible light and other currently studied radiations [9, 36].

Given the evidence of global warming, the aging population, and the increased number of cases of skin neoplasms, a systematic and broad photoprotection is recommended as the primary preventive and therapeutic strategy against skin cancer and photoaging, especially for individuals with light skin phototypes, multiple atypical nevi, and previous skin cancer history, outdoor workers, children, and immunologically vulnerable people.

Athletes in particular should be prepared, equipped, and up-to-date on protection practices and the effects of UV radiation on health [1, 12]. Outdoor activities are subject to the dangers, risks, and unpredictable situations associated with natural environments, such as sudden climate variations.

The future of photoprotection in sports will probably include an evolution in the composition and design of sports uniforms and accessories, changes in the times of competitions, the development of photoprotective agents with enzymes to remove or repair DNA damage, and new systemic sunscreens.

Recent research has made possible a better use of renewable energy resources, such as solar power, and has encouraged more conscious use of natural resources. Moreover, there are increased investments in studies of more efficient local and systemic photoprotection methods for the prevention, reduction, or repair of damage caused by sun exposure, with the development and improvement of several photoprotection technologies.

Educational campaigns have been carried out in many countries to promote healthier behaviors and the choice of times of lower solar radiation for the performance of outdoor activities, sports training, work shifts, and school recess, as well as the use of tree shadow, parasols, or covers aimed at habit changing and a more global protection.

Research, innovation, smart technologies, and educational investments point to a promising future in photoprotection. New programs with strong social awareness components will probably be created to educate the population, especially children. In addition, more efficient and objective public health policies should be implemented to reduce skin cancer rates and improve our quality of life.

Conclusion

When used properly and cautiously, sun exposure can bring physical and psychological benefits. Uncontrolled and unprotected exposure to radiation, however, causes damage to the skin, eyes, and health. The conjunctive use of different photoprotective resources and daily preventive measures should be advised and implemented in daily activities from childhood onward to minimize risks and improve the quality of life. The whole society, and particularly physicians, must play an important role in the transmission of knowledge about healthy sun exposure to the population.

Glossary

Malignant skin neoplasm a malignant epithelial neoplasm. The most common types are basal cell carcinoma and squamous cell carcinoma.

Melanoma A malignant melanocytic neoplasm that can occur on any part of the body. It has a rapid growth rate and high metastasis potential, and may be fatal.

Photoaging The superimposition of chronic sun damage on the intrinsic skin-aging process.

Photodamage Skin changes resulting from UV light exposure.

Photoprotection Measures used to avoid or interfere with solar radiation, reducing its deleterious effects.

Phototype Characterization of the skin according to its color and how it reacts to sun exposure. In brief it has been classified by Fitzpatrick into: (a) fair skin that never tans and is highly susceptible to sunburn (phototypes I and II); (b) white to brown skin with intermediate pigmentation (phototypes III and IV); (c) dark skin with accentuated pigmentation (phototypes V and VI).

Sunburn The main acute skin reaction to excessive sunlight exposure. It can evolve into erythema, edema, blistering, peeling, and skin pigmentation. The face, neck, and trunk are more sensitive to sunburn than the limbs. The development of erythema is influenced by factors such as duration of exposure, phototype, age, diet, health characteristics, and atmospheric conditions (wind, heat, humidity, clouds).

Sunscreens (or sun filters) Substances applied to the skin surface in different presentations, which contain in their formulation ingredients capable of absorbing, reflecting, or scattering UV radiation.

Ultraviolet index (UV index) A scale for measuring the amount of UV radiation reaching the earth's surface and posing a health danger to all humans, not only individuals with certain skin phototypes. The higher the UV index, the greater the potential for damage to the skin. Its aim is to help people prevent excessive sun exposure at their current geographic position.

Ultraviolet radiation Part of the Sun's light that reaches the earth and the human skin, having both positive and negative health effects.

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Dermatology and Sports

50

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Key Points

- Herpes gladiatorum and tinea gladiatorum are common cutaneous infectious on the face, neck, trunk, and upper limbs that occur more frequently in men performing contact sports.
- Traumatic cutaneous lesions are extremely common among athletes. These reactions may vary in location, distribution, and intensity depending on the sport modality, and history taking is crucial for recognition.
- Sport-induced urticaria is a type of physical urticaria related to angioedema or anaphylactic reactions, which may be food or medication dependent.
- Dermatologic prescriptions may contain substances prohibited by some sports, and dermatologists should contact sports federations whenever necessary.

Introduction

To perform physical activities is nowadays considered an appropriate behavior to achieve good health, leisure, and quality of life. An increasing number of individuals seek sports participation for these reasons and also as a professional career. Nevertheless, because of different personal conditions of the athlete or sports-related and environmental aspects, distinct cutaneous injuries may occur during participation.

Sport-related skin diseases or conditions can be caused by physical, chemical, or biological agents alone or in association. Preexisting medical conditions may also contribute to cutaneous injuries. Most cutaneous reactions are mild and rapid, and easy recovery is expected, although some may be relapsing and have an impact on the athlete's performance. Some cutaneous diseases may also lead to exclusion of athletes from sports events. Consequently, recognizing and controlling sport-associated dermatologic conditions can be also relevant not only to ensure good medical conditions in athletes but also to improve their performance. In this chapter, some of the main sports-related dermatologic diseases and conditions are described.

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State of the Art

Lesions Caused by Infectious Agents

In sports, an infectious process has individual and collective impacts as it hinders, limits, or prevents practice. The risk of contagion is greater and more worrying among athletes participating in team and contact sports. It is essential that athletes, coaches, and the multidisciplinary care team have the knowledge to observe skin integrity aimed at preventing injury and providing appropriate action, minimizing transmission within the team [1–4]. Thus, it may be necessary to exclude an athlete from a sports event in order to preserve the health of the others. Immunocompromised players are more vulnerable to infections and, similar to children, pregnant women, and Paralympic athletes, require specific care [3, 4]. Bacterial and fungal infections are common in obesite and diabetic individuals, and have implications for physical activity because they cause pain, discomfort, and difficulty or limitation of movement [5]. Strategies to promote skin health may improve the quality of life of different types of athletes and result in better performance.

Herpes Gladiatorum

This infection is caused by herpes simplex virus in athletes practicing contact sports. It is characterized by grouped vesicles or an erythematous base associated with paresthesia, affecting mainly the cervical and upper thoracic regions of boxers and wrestlers. The main predisposing factors are body contact, chafing caused by uniforms, local trauma, stress, and sun exposure. Clinical diagnosis can be complemented by Tzanck smear, histopathology, and serology. Oral treatment comprises acyclovir (400 mg three times daily or 200 mg five times daily), famciclovir (250 mg three times daily), or valacyclovir (1 g three times daily) for 5 days, on average. In contact sports, when the affected areas are exposed the lesions should be covered or occluded, and there may be a need to exclude the athlete from competition [3].

Common Warts

Warts are seen with some frequency on the hands and feet of athletes of sports whose impact is greater in these areas. In sports such as running, martial arts, and water activities that involve the use of collective dressing rooms, warts are more common in the lower limbs. Pool users, especially if they are atopic individuals, tend to have warts caused by friction, maceration, and microtrauma in the plantar region. Clinical diagnosis is made by localized hyperkeratosis, pinpoint black spots, and disruption of the skin lines in the affected area. There are several therapeutic options with varying success rates, such as chemical cauterization, cryotherapy, electrocoagulation, and use of imiquimod, depending on severity and location. Extensive and exophytic lesions may require surgery and histopathology. In contact sports, when the affected areas are exposed the lesions should be covered or occluded, and there may be a need to exclude the athlete from competition [3].

Tinea Corporis Gladiatorum

This is a dermatophytosis that presents a different clinical pattern, frequently detected in men performing contact sports, mainly wrestlers. The most exposed and affected areas are the face, neck, trunk, and upper limbs. Transmission occurs via skin-to-skin contact or through contaminated objects and surfaces. Clinical diagnosis is based on mycologic examination and culture, usually with identification of *Trichophyton tonsurans*. Lesions are scaly and itchy erythematous plaques, and may assume epidemic proportions in the wrestlers' community. It is treated with topical (ketoconazole, isoconazole, terbinafine, etc.) or systemic (griseofulvin 500 mg/day, itraconazole 100–200 mg/day, fluconazole 150 mg/day, or terbinafine 250 mg/day) antifungals until the lesions heal, along with health measures. If lesions cannot be covered, the athlete will be unable to compete until cured [6].

Tinea Pedis

Tinea pedis, commonly known as athlete's foot (Fig. 50.1), is not exclusive to athletes, although it is common in certain sports. *Trichophyton rubrum* and *Trichophyton mentagrophytes* are mainly responsible for tinea pedis alone or combined with onychomycosis and tinea cruris. This mycosis is favored by individual predisposition, moisture resulting from excessive foot sweating, occlusive shoes, showering in public places, walking barefoot on communal floors, and sharing equipment and towels. Associations with yeasts and bacteria are

Fig. 50.1 Tinea pedis: athlete's foot (Courtesy of Dr. Renan Bonamigo)

described, and an interdigital attack increases the risk for development of erysipelas or cellulitis of the lower limb. Tinea pedis symptoms are erythema, scaling, fissures and blisters on the feet, associated with itching, discomfort, and social and functional limitation. Clinical diagnosis can be confirmed by direct mycologic examination and culture. Prophylactic measures are essential (wearing sandals in wet environments, changing shoes and socks, drying feet and interdigital areas, not sharing towels or personal items), and treatment can be carried out with topical or systemic antifungals, according to the extent and severity of the clinical picture [7, 8].

Onychomycosis

The highest percentages of nail injuries in athletes are associated with trauma. This condition favors the penetration of fungi and bacteria. The fungal lesions may be restricted or associated with cutaneous lesions. Onychomycosis can evolve to loss of the nail, ingrown toenail, local pain, and limitation of sports movements of the feet [5, 9, 10]. It is necessary to differentiate this from other nail disorders [8, 11].

Swimmer's Ear

Swimmer's ear is caused by bacteria, such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Clinical diagnosis is based on symptoms of itching, pain, and redness in the ear canal. Predisposing factors are maceration resulting from long immersion periods in the water leading to ear wax decrease and external ear pH alteration, frequency and quality of activities, pool water treatment, and hygiene. The treatment is based on removing debris from the ear canal and

its acidification using 2% acetic acid in propylene glycol. Relapsing, complicated, or severe cases may cause temporary or permanent limitation on carrying out professional water activities [12].

Sea Bather's Eruption

This dermatitis is caused via contacting marine species of *Cnidaria phylum* (jellyfish, Portuguese man-of-war, sea anemones, corals). It has been described by swimmers and athletes from the Caribbean Sea, Mexico, Australia, and Brazil. Therefore, its importance is growing in recreational and professional water sports activities. Clinical diagnosis is based on body examination for erythematous papules, and pruritic lesions in areas covered or not by the bathing suit after swimming in the sea. Treatment consists in getting out of the sea and applying acetic acid on the affected area. Corticosteroids, antihistamines, and menthol lotions are least effective. Spontaneous regression of the lesions occurs in a few days or up to 2 weeks. Depending on the sea conditions, swimming or competitions should be discontinued [13–15].

Cercarial Dermatitis

People who practice water activities in lakes, streams, rivers, and weirs are subject to skin lesions caused by cercariae of *Schistosoma mansoni* parasites. Diagnosis is made based on epidemiologic history and body examination for erythematous itchy rashes in areas not protected by clothes a few hours after being in contact with water. The symptoms disappear spontaneously or after administering ivermectin orally. Taking into consideration the risks of diseases and accidents involves in this recreational or adventure practice, popular especially in the summer, hygiene orientation should be taught to swimmers and athletes [15].

Other Skin Infections

It should be noted that infectious cutaneous manifestations in athletes vary in their etiology, origin, frequency, and intensity. They include molluscum contagiosum, cutaneous larva migrans, pitted keratolysis, impetigo, folliculitis, scabies, lice infestation, and various mycoses. These diseases may be disguised or worsened by traumatic disorders, inflammatory processes, environmental factors, and pre-existing dermatoses [16].

Most of these conditions are mild and temporary, while others are recurrent and may have an unfavorable outcome. Early recognition and treatment are essential, considering the need for the professional athlete to recover as quickly as possible. One should note the need to exclude the athlete from competition may arise if the condition is contagious [3].

Lesions Caused by Traumatic Conditions

Friction Blisters

The causes of blister development are friction and local skin trauma, commonly on the feet, due to ill-fitting shoes. Other risk factors include various sports equipment (racquets, bats, sticks, bars, etc.) when used in extended and nonideal conditions. The diagnosis is not challenging once the blisters are easily recognized for their discomfort and pain, plus the risk of secondary infection. Treatment consists of hygiene, protection of the affected area, and proper draining if necessary. Prevention of blisters requires comfortable and athlete-adjusted equipment as well as protection on the areas that undergo higher friction [3, 17–19] (Fig. 50.2).

Fig. 50.2 Friction blisters (Courtesy of Dr. Renan Bonamigo)

Calluses and Callosities

These are known as an innate protection mechanism for areas that suffer from constant trauma and friction, sometimes even being the natural evolution of recurrent blisters. Treatment is indicated only if interference of the function is recognized, and includes chemical or physical excision. Prevention with appropriate socks, shoes, and insoles is recommended [5, 10, 20].

Calcaneal Petechiae (Black Heel)

Petechiae are the result of small hemorrhages caused by microtraumatism to the cutaneous capillaries, in areas that suffer from the association of thin fatty tissue, repeated trauma, and bone proximity. They are most common in the calcaneus when practicing sports such as tennis, basketball, and running, caused by rough stop-and-start motions. The lesions may occur on the hands when practicing golf, baseball, weight lifting, or gymnastics. Lentiginous acral melanoma is the differential diagnosis, and dermoscopy may be useful to exclude any suspicion. The lesions disappear if the evolved sport activity is ceased [17, 21, 22].

Jogger's Toe

Subungual or periungual hematoma of the toenails may occur as a result of significant nail trauma (Fig. 50.3), associated with onycholysis and thickening of the nail. The use of poorly adapted or nonideal shoes while practicing sports is the main cause. Painful hematoma can be drained if necessary. Prevention includes the use of appropriate and well-fitting athletic wear, as well as adequate protective silicon insoles to cover the toes [5, 10, 17].

Piezogenic Pedal Papules

These are skin-colored, occasionally painful papules located on the medial or posterolateral side of the heels. Better visualized when standing, their prevalence is found to be up to 10%. Usually symptomatic in long-distance runners, the papules arise from subcutaneous fat herniations through the connective tissue. For painful papules, compression stockings and heel cups are useful [17, 23–25].

Fig. 50.3 Jogger's toe (subungual hematoma) (Courtesy of Dr. Renan Bonamigo)

Jogger's Nipples

Pain, erosion, and eventual bleeding result from irritation caused by repetitive friction between runners' shirts and their nipples, especially when using coarse-fiber T-shirts. Treatment is easy, for consisting simply of removing the cause. Avoiding such fibers, applying petroleum jelly, or the use of adhesive bandages are good options to prevent this condition. Soft-fiber and well-adapted bras are useful for women [3, 17, 20].

Knuckle Pads

Chronic compression on the knuckles may lead to the development of fibrous skin nodules. Soccer players may present such callosities on the feet, whereas in boxers the nodules occur between the phalanxes of fingers [20, 26].

Environment-Related Cutaneous Conditions

It is common to sports participants to use mandatory equipment, shoe gear, or clothes. This can lead to athletes suffering cutaneous reactions exacerbated from their use or even triggered by them. Some of these conditions might be due to allergic or irritant contact. In addition, weather conditions or even nutritional aspects may aggravate clinical symptoms or diseases. Some of the most relevant conditions are described here.

Contact Dermatitis

Every sport has peculiar aspects as regards its necessary equipment and clothes. Therefore it is common for athletes to present with allergic or irritant contact dermatitis [27]. Allergic contact dermatitis depends on an individual sensitizing predisposition, while irritant contact dermatitis may occur in any athlete depending on time of exposure to a specific substance. Initial clinical suspicion may show after asking the patient appropriate questions about sports participation. Water sports are mostly involved. It is frequent to observe reactions to rubber material such as goggles, underwater masks, and diving suits [28, 29]. Epicutaneous tests might be important in suspicious cases. Allergens such as phenylenediamine and thiourea are good examples of substances involved in the rubber manufacturing process. Topical medications, resins, and inks are other potential causes of dermatitis. Irritant contact dermatitis due to plants might be observed in golfers or hikers. Different sport equipment may also be involved in irritant contact dermatitis, and a careful anamnesis might help to elucidate the scenario. Even the athlete's own body may cause, for example, "swimmer's shoulder" resulting from unshaven hair. The therapeutic approach consists in recognizing the allergenic or irritant agent, and appropriate use of topical steroids and oral antihistamines [27].

Xerosis

Athletes who partake in water sports, especially swimmers, are prone to dry skin. They stay in the water for long periods and lose essential cutaneous oils. Taking hot-water showers after exercise

together with soaps worsens the scenario, especially in atopy patients. This is the major cause of pruritus in athletes. Shortening the duration of showers and reducing the water temperature in combination with application of ointments may be a sufficient therapy [3, 27].

Mechanical Acne

This particular acne variant has been described in different sports such as American football, wrestling, and gymnastics. Pre-existing acne is not necessary for its development. It occurs as a result of continuous frictional movements or pressure by sports equipment (helmets, clothes) with occlusion, heat, and humidity [30]. Clinical aspects are very typical, presenting erythematous papules and pustules on body sites associated with equipment-induced pressure or friction. The posterior aspect of the neck and the back are common affected areas. It is important to rule out anabolic steroid use in rapid-onset acne [31]. Recent mild intake has been associated with acne worsening [32]. Moreover, whey protein consumption also precipitated acne development, which was relieved after supplementation suspension [33]. Therefore, nutritional aspects in athletes with acne should always be asked after. Treatment is based on reducing friction or pressure from the equipment and regular acne medications depending on its extent and duration. Total involution of the lesions may occur only at the end of the sport season [27].

Urticaria

Sport-induced urticaria is a type of physical urticaria that, though rarely, can lead to emergency medical situations such as angioedema or anaphylactic reactions [34]. It may be triggered by intense or mild physical exercises. The symptoms may occur just after sport initiation and vary from itching, flushing, burning sensation, and hives to angioedema and cardiovascular collapse [35]. Ninety percent of the athletes refer pruritus as the first symptom. Joggers are particularly affected. Sport-induced urticaria may also be triggered by ingestion of specific foodstuffs (e.g., wheat derivatives) or medications (aspirin or nonsteroidal anti-inflammatory agents) before

exercise [36]. Athletes are also more prone to develop other urticaria variants such as aquagenic, solar, heat, or cold urticaria. Sport-induced urticaria patients should not exercise alone. Use of antihistamines before sport participation may prevent symptoms. If presenting symptoms, patients should suspend exercise immediately. Other measures may be necessary, such as symptomatic medications or subcutaneous epinephrine [3].

Miscellaneous

Striae

Stretch marks are very common in isometric sports participants (70% of female adolescents and 40% of boys), although abrupt striae may also occur in anabolic steroid users. The former situation may be suspected if other androgenic aspects are present, such as acne, oily skin, and androgenetic alopecia. Weightlifting, bodybuilding, gymnastics, and fighting sports are especially associated with striae development caused by skin distension and muscular hypertrophy. Treatment is difficult and should be the same as for other causes. Options include topical tretinoin and laser therapy [3, 37].

Green Hair

Green hair is particularly common among swimmers. The green color is due to copper impregnation and not chlorides as frequently attributed. Increased copper levels in the water may occur because of old pipes or copper-containing algaecides. Showering immediately with shampoos and rinse creams after leaving the swimming pool should be sufficient to avoid the condition [27].

Skin Cancer and Sun Protection

As many sports are performed outdoors, sun protection is always a leading concern among health professionals regarding athletes. Several reports demonstrate that athletes who compete in this scenario receive considerable ultraviolet (UV) doses because of training and competition schedules. UV dosimetric studies have demonstrated

that some sports such as skiing, mountaineering, cycling, or triathlon are associated with extreme cumulative UV doses [38]. Moreover, outdoor sports may lead to UV-associated skin lesions even in children. In a cohort it was observed that the nevus count and acquired nevus count were higher in children who practiced outdoor sports [39]. UV radiation is well known as one of the major environmental risk factors for skin cancer. Therefore, some athletes may have an increased risk of developing skin cancer. Indeed in marathon runners it was demonstrated that presence of lentigines correlated with type of sportswear and intense training schedule had an impact on the number of nevi, which are well recognized as melanoma risk factors [40]. In another survey marathon runners presented an increased risk of developing melanoma and other skin cancers in comparison with controls [41]. Fair-skinned athletes competing for the Brazilian national team in the 2003 Pan-American Games stated that they had more sunburn episodes in leisure activities than in sport participation. Therefore, athletes should be educated to adopt sun-protection habits during both periods to prevent UV damage [42]. Prevention strategies to avoid sun exposure include wearing hats, long pants, and long-sleeved shirts, using sunscreens with sun protection factor 30 or higher and avoiding peak UV exposure hours. Unfortunately, the particularities of some sports raise difficulties in dealing with sun protection. It is always important to educate athletes about sun care to improving their sun-care habits. Not only athletes but also the spectators of sporting events should also be very cautious about sun protection, as the duration of events may be sometimes prolonged and occur during peak UV hours [38, 39, 43].

Doping Control and Dermatology

As athletes must regularly undergo doping control tests, dermatologists should be aware of their prescription in this scenario. Some frequently prescribed medications by dermatologists are prohibited in professional sports events. The use of these substances may lead to severe suspensions or even elimination from the sport. The WADA (World Anti-Doping Agency) publishes online (http://www.wada-ama.org) the prohibited substances list every year. Dermatologists should always contact sports federation medical doctors if any substance from the list needs to be used for medical reasons. It may be possible for the athlete to compete using a substance present on the list as long as all the necessary procedures and forms are applied and approved before he/she takes part in sports training or competition ("therapeutic use exemption").

Perspectives: Final Remarks

Sports and dermatology are connected in different ways. Dermatologists should be aware of these scenarios so as to educate athletes about preventive measures against major sport-related skin diseases and to detect and treat them, and finally to avoid harming the athletes through inadequate prescriptions for professional athletes.

Glossary

Flushing Sudden vasodilation by different mechanisms causing skin erythema.

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Dermatosis in Conflict Zones and Disaster Areas

51

Rosana Buffon

Key Points

- The increasing number of natural disasters and armed conflicts in recent decades carries a wide range of clinically relevant dermatoses
- Dermatologic care is presumably required when multiple medical and social problems arise shortly after the onset of an emergency
- About two-thirds of the total deaths in postconflict situations are caused by communicable diseases, some of them skin-related
- Poverty, malnutrition, displacement, poor infrastructure, and inadequate disaster preparedness efforts are the leading causes of communicable skin diseases among refugees
- In response to medical emergencies and disasters, teledermatology has been used to deliver dermatologic care in remote locations

Introduction

At a glance it seems nonsense to include a dermatologist among emergency doctors in a hotspot of a conflict zone or disaster area. It makes sense if in such conditions a dermatologist is called later for elective consultation or intervention. Dermatologic care is presumably required when multiple medical and social problems arise shortly after the onset of an emergency. For instance, a dermatologist's opinion is helpful in complex cases of war burns and outbreaks of measles and cutaneous leishmaniasis, and for specific diagnoses that are not easily detected and managed by emergency doctors (Table 51.1). Apart from a role as a specialist after an emergency, it is opportune to make dermatologists aware of potential risks and imminent skin damage secondary to natural disasters and armed

Table 51.1 Main dermatoses in conflict zones and disaster areas

Main dermatoses in conflict zones and disaster areas
Damage caused by low temperatures
Burns
Wounds
Vitamin deficiencies
Insect bites and other stings
Viral exanthems
Parasite and bacterial infections
Fungal infections
Sexually transmitted diseases
Aggravation of chronic skin diseases

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conflicts, since such conditions are usually unpredictable or unplanned. Understanding the true burden of skin diseases in such situations is difficult as there are many political, logistical, and ethical barriers to conducting programs, surveillance, and research. In fact, the medical literature available for this topic is scarce. Available data are based on reports of nongovernmental organizations or philanthropic foundations, international organizations, volunteering fieldwork, and personal experiences.

By definition, a disaster is a disruption of a society resulting in widespread human, material, or environmental loss that exceeds the affected society's ability to cope by using local resources [1]. Disasters include earthquakes, volcanic eruptions, landslides, tsunamis, floods, and droughts. Populations in developing countries are disproportionately more affected because of poverty, lack of resources, poor infrastructure, and inadequate disaster preparedness efforts [2].

During recent decades, the scale of disasters has expanded owing to increased rates of urbanization, deforestation, and environmental degradation, as well as the intensification of climate variables such as higher temperatures, extreme precipitation, and more violent wind and water storms [3]. The 2004 Indian Ocean tsunami was among the deadliest natural disasters in human history, with at least 230,000 people killed or missing in 14 countries bordering the Indian Ocean [4]. The 2010 earthquake in Haiti killed around 225,000 people in a matter of minutes, destroyed health care facilities, and left many homeless [3]. Deaths associated with natural disasters, particularly rapid-onset disasters, are overwhelmingly due to blunt trauma, crush-related injuries, or drowning. Deaths from communicable diseases after natural disasters are less common [2].

In addition, tens of thousands of other people are dying in armed conflicts around the world, even as the number of conflicts falls, according to an authoritative study that attributes the rising death toll to an inexorable intensification of violence [5]. Sixty-three armed conflicts led to 56,000 fatalities in 2008, whereas 180,000 people died in 42 conflicts in 2014. The numbers reflect the extremely violent fighting in Syria and Iraq and the increasing deaths in Afghanistan following the withdrawal of Western combat troops. The Israeli–Palestinian conflict killed 2500 people in 2015, mostly civilians, while fighting in Libya, Yemen, and the Central African Republic also contributed to the rise in overall deaths [5]. In such settings, health systems often collapse or become nonfunctional. Overcrowding, high population density in rudimentary shelters or camps, famine, inadequate safe water and sanitation, and poor vaccination status among victims increase the risk of infectious disease spread [6] and result in higher morbidity and mortality, especially among children.

In 2016, according to Médecins Sans Frontières (also known as Doctors Without Borders), skin diseases and burns are among the main pathologies observed in rescued persons in the Mediterranean Sea, most of them victims of the armed conflicts in Africa and the Middle East [7]. Millions of refugees are detained in reception centers for immigrants and asylum seekers, where physical conditions are extremely poor. In 2013–2014 more than 8% of patients' complaints were related to skin diseases [8]. Again, internal displaced persons (IDPs) who are resident in camps have increased vulnerability to skin infections, environment-associated disorders such as xerosis cutis and eczema, and diseases of psychosomatic origin [9]. Skin infections including scabies, along with acute respiratory tract infections and acute diarrhea, are the leading cause of morbidity [10].

Advances in small-arms technology and struggles over natural resources of international value (oil and rare minerals) make conflict resolution challenging. It is difficult to know whether the nature of conflicts has changed, but recent wars provide evidence of the targeting of health facilities to weaken opposition forces and populations. Refugees cross national borders and are legally entitled to assistance in United Nations (UN)-managed camps but, increasingly since the mid-1980s, people have been unable to cross international frontiers and so remain internally

displaced. This population are often at higher risk for malnutrition and disease than residents or refugees [11].

State of the Art

Skin Injuries Related to Chemical Warfare

Blistering or vesicant agents are toxic compounds that produce skin injuries resembling those caused by burns [12]. With its characteristic garlic smell, sulfur mustard (SM) is the vesicant with the highest military significance since its use in World War I. Its last military use was in the Iran–Iraq war. SM injured more than 100,000 Iranians, one-third of whom are still suffering from lingering effects [13]. In modern times it remains a threat on the battlefield as well as a potential terrorist threat because of its simplicity of manufacture and extreme effectiveness [14].

Skin disorders are one of the major complications in SM exposure. The most common signs and symptoms are itching (78%), dry skin (60%), burning sensation (60%), blisters (25%), scarring (18%), dermatitis (13%), and pigmentary changes (hypo- or hyperpigmentation, 11%). Skin injury ranges from sunburn-like erythema to vesicles, which coalesce into blisters. Depending on the level of contamination, SM burns can vary between first- and second-degree burns, although they can also be every bit as severe, disfiguring, and dangerous as third-degree burns. Exposure to SM was lethal in about 1% of cases. Its effectiveness was as an incapacitating agent [13]. Other vesicants of lesser military importance include nitrogen mustard, Lewisite, and phosgene oxime, which are not discussed in detail here.

The use of poison gases, including SM, during warfare is known as chemical warfare, which was prohibited by the Geneva Protocol of 1925 and also by the later Chemical Weapons Convention of 1993. In September 2015 a United States official stated that the rebel militant group ISIS was manufacturing and using SM in Syria and Iraq, which was allegedly confirmed by their group's head of chemical weapons development, Sleiman Daoud al-Afari, who has since been captured [15].

War-Related Burn Injuries

War burns have been described for more than 5000 years of written history, and fire was probably utilized as a weapon long before. Burns and injuries from shrapnel fragments or small arms are the most common wounds to be expected in modern conventional armed conflicts [16]. The overall incidence of burns in current military operations has nearly doubled during the past few years. Unfortunately, civilians are becoming the major targets in modern-day conflicts, accounting for more than 80% of those killed and wounded in present-day conflicts. The provision of military burn care mirrors the civilian standards; however, several aspects of treatment of war-related burn injuries are peculiar to the war situation itself and to the specific conditions of each armed conflict [17].

The critical issue, however, is not the exact number of casualties, but whether the needs of the patients exceed the resources of the health-care entity at the time they are required. If the facility, materiel, or personnel are hindered or destroyed, there may be insufficient surge capacity to manage the casualties [14]. War-related burn injuries, even among civilians, are unlikely to be the only trauma and are generally more extensive, deeper, more complicated, associated with inhalation injuries, and undertreated in comparison with the accidental burns in our everyday life. Nevertheless, burn injuries that were fatal just a few years ago no longer are, although even with rapid and proper response, burns are still complicated injuries that require lengthy therapy and treatment, particularly when they are complicated by other serious injuries. As the technology of weaponry advances, the number and severity of burn injuries will certainly increase [16].

Dermatology and Bioterrorism

A bioterrorism attack is the deliberate release of viruses, bacteria, or other germs (agents) used to cause illness or death in people, animals, or plants. These agents are typically found in nature, but it is possible that they could be changed to increase their ability to cause disease, make them resistant to current medicines, or increase their ability to be spread into the environment [18]. Biological agents are easy to develop as weapons, are more lethal than chemical weapons, and are less expensive and more difficult to detect than nuclear weapons [19]. The intentional dispersal of anthrax through the United States Postal Service that followed the terrorist attacks of September 11, 2001 brought these issues into clear focus. Five of the 11 victims (45%) of inhalational anthrax succumbed in the Amerithrax mailings of 2001 [20].

Anthrax and smallpox (*Variola* virus) are the most common skin disease agents with the potential of biologic terrorism. A study conducted by the World Health Organization (WHO) showed that Anthrax was somewhat unique in its ability to produce widespread mortality [21]. Smallpox was historically a significant cause of human suffering and death worldwide, responsible for as many as 50 million cases per year in the middle of the last century. The WHO declared smallpox to be eradicated in 1980 after a monumental worldwide vaccination campaign. Significant concern remains that existing laboratory-based *Variola* virus isolates could be reintroduced as a weapon to target an increasingly susceptible population. With an increasing immunologically naive population and the ease of global travel, there is concern that smallpox would spread faster than it has historically [14].

The consequences of using biological weapons are many. They can rapidly produce mass effect that overwhelms services and the healthcare system of communities. Most of the civilian population is susceptible to infections caused by these agents, which are associated with high morbidity and mortality rates. The resulting illness is usually difficult to diagnose and treat early, particularly in areas where the disease is rarely seen.

One kilogram of anthrax powder has the capability to kill up to 100,000 people depending on the mechanism of delivery [22].

Communicable Skin Diseases and Epidemics in Displaced Populations

Disasters and armed conflicts contribute to increased population displacements and densities in camps, creating new conditions for the spread of infectious diseases. In effect, about two-thirds of the total deaths in postconflict situations are caused by communicable diseases because of displacement, malnutrition, and limited access to basic needs [23–25]. In a study published by Salazar, communicable diseases were found to be the predominant syndrome group after three main natural disasters – a flood, an earthquake, and a typhoon – in the Philippines in 2013. Skin communicable diseases were at the top of most common syndromes found [26].

A communicable disease is defined as an illness that arises from transmission of an infectious agent or its toxic product from an infected person, animal, or reservoir to a susceptible host, either directly or indirectly through an intermediate plant or animal host, vector, or environment. An epidemic, or outbreak, occurs when there are more people suffering from a particular illness than would normally be expected. Children younger than 5 years of age (usually about 20% of the displaced population) and the elderly are at the highest risk of morbidity and mortality from infectious diseases, particularly the malnourished [25].

The availability of safe water and sanitation facilities, the degree of crowding, the underlying health status of the population, the size and characteristics of the population displaced, the nutritional status of the displaced population, the level of immunity to vaccine-preventable diseases such as measles, and the availability of healthcare services all interact within the context of the local disease ecology to influence the risk for communicable diseases and death in the affected population [2]. For instance, recurrent scabies outbreaks

observed in many detention facilities are indicative of the substandard conditions, as the spread of the disease is directly linked to poor sanitary conditions [8]. Because developing countries may lack resources, infrastructure, and disaster-preparedness systems, they may be disproportionately affected by disasters.

A wide range of skin diseases may be observed according to different phases of a natural disaster. The impact phase occurs from 0 to 4 days, during which extrication of victims and treatment of immediate soft tissue infections takes place. Hypothermia, heat, illness, and dehydration are characteristic of this phase. In the postimpact phase, which takes place from 4 days to 4 weeks after the disaster, airborne, foodborne, waterborne, and vector diseases are seen. Examples of skin diseases in this phase are measles and varicella. The recovery phase begins after 4 weeks, and diseases with long incubation periods, vectorborne, and chronic diseases emerge. Leishmaniasis is an example of skin disease caused by organisms with long incubation periods [27].

Migrants often come from communities affected by war, conflict, or economic crisis and undertake long, exhausting journeys that increase their risks for communicable diseases, particularly measles, and food- and waterborne diseases. This is also true for vectorborne diseases in the Mediterranean area, such as leishmaniasis, with outbreaks recently reported in the Syrian Arab Republic [28].

The length of time that people spend in temporary settlements is an important determinant for the risk of disease transmission. The prolonged mass settlement of refugees in temporary shelters with only minimal provision for essential personal hygiene is typical of a situation that may cause epidemic outbreaks of infectious diseases. Camps established to provide food relief during famine are a special case, as large numbers of people who are already weak and possibly ill are likely to remain in such camps for a long time [29].

Measles Outbreaks

Measles is an important public health concern during disasters involving massive population displacements that end up living in camps. The WHO recognizes refugees as one of the high-risk groups for measles outbreaks. Several outbreaks have been reported among refugees and in other emergency settings [30–32]. Overcrowding is associated with the transmission of higher infectious doses of measles virus, resulting in more severe cases of clinical disease, which makes measles more often the leading cause of mortality among children in refugee populations. Despite measles control strategies in refugee settings, case-fatality rates (CFR) as high as 34% have been reported. In contrast, measles CFR in stable populations are around 2% [33]. The risk of measles transmission after a natural disaster is also dependent on baseline immunization coverage among the affected population, and in particular among children under 15 years of age [2].

Historically, measles outbreaks have occurred among populations displaced in Africa and Asia where low routine vaccination coverage, even for the general population, has been reported. Almost all measles outbreaks occur in postconflict situations alongside collapse of the health system and disruption of the immunization program [33]. Several conflict-affected countries reportedly have measles coverage below 50%, and widespread outbreaks have been reported in Ethiopia, the Democratic Republic of Congo, and Afghanistan [25].

The highest incidence rate (25.5%) for a measles outbreak was described for Vietnamese children in Hong Kong camps where housing was cramped, consisting of large huts that housed approximately 250 refugees on three-tier bunk beds [34]. The only outbreak that occurred among those with a high coverage of 95% was the outbreak among the tsunami victims. It was suggested that the single-dose vaccination strategy might have been responsible for this outbreak [35].

Measles is an extremely serious disease in severely malnourished children. The age group from 5 to 15 years has been the most affected. Measles impairs the immune system for several months after infection, worsens vitamin A deficiency, and is a precipitating cause of xerophthalmia. In addition, measles often results in rapid

and significant weight loss and can trigger cases of kwashiorkor. Severe complications of measles, such as pneumonia, are common in malnourished patients, and the case fatality rate can be as high as 30%. Vitamin A supplements together with measles vaccination have been recommended to minimize mortality [36–38].

Skin and Soft-Tissue Skin Infections

Wound infections are common after disasters. The destruction of the regional health infrastructure, the inability to wash wounds with clean water, and the inability to treat individuals with topical or systemic antimicrobial agents can all lead to severe wound infections, even if the initial trauma was relatively minor [14]. First responders are often not medically trained and, although well intentioned, the treatment they provide is often compromised by a misconception that wounds should be closed to enable them to heal [39]. In addition, damage to the local healthcare infrastructure can compromise the ability to properly treat contaminated wounds, resulting in severe, often polymicrobial, infections [40]. Sepsis with or without necrotizing fasciitis has being frequently seen following flood and tsunami wounds and has been associated with more than doubling of mortality [41]. Among survivors of the tsunami in Thailand in December 2004, traumatic wounds were contaminated with mud, sand, debris, and seawater and had an infection rate of 66.5%. Most wounds (45%) had polymicrobial infection with Gram-negative rods such as *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus*, and *Pseudomonas* species. The risk of wound infection increased with size of the wound and presence of an open fracture [42].

Although considered a common and treatable problem in the Western world, impetigo patients are triaged as urgent in refugee camps and among internally displaced populations, especially if victims are malnourished (Fig. 51.1). Impetigo can progress rapidly from a minor skin infection to septicemia when micronutrient deficiencies and severe malnutrition exist [14]. In 2005, among hurricane Katrina evacuees from the New Orleans area, a cluster of infections with methicillin-resistant *Staphylococcus aureus*

Fig. 51.1 A female newborn with diffuse bullous impetigo admitted to the inpatient department (IPD) of MSF clinic in Doro refugee camp, South Sudan, 2013

(MRSA) was reported in approximately 30 pediatric and adult patients at an evacuee facility in Dallas, Texas [43]. Wounds are at particular risk of becoming infected by MRSA because of conditions that are likely to occur after a natural disaster, such as close skin-to-skin contact with other individuals, use of contaminated items to treat wounds, lack of cleanliness, and crowded living conditions.

The refugee camps are considered the ideal condition for scabies infestation. Patients frequently present with scabies in the outpatient department, and a few "scabies outbreaks" have been reported in refugee populations. Although scabies-related mortality is very low, this is a common health problem among refugees [44].

Disaster-associated fungal infections are uncommon but they are becoming increasingly recognized, and are typically attributable to the impact phase of a disaster because such infections primarily result from inhalation or cutaneous inoculation of fungal spores directly from the environment [45]. Events affecting larger areas,

such as earthquakes, tsunamis, and tornadoes, have been linked to the occurrence of fungal infections. Mucormycosis is perhaps the most recognized example of postdisaster fungal soft tissue infection. Necrotizing fasciitis can result, and case-fatality rates of ≈30% are frequently described, although early diagnosis and treatment has been shown to lead to better outcomes [46].

An unusual outbreak of coccidiomycosis occurred following the January 1994 southern California earthquake. The infection is not transmitted from person to person but is caused by the fungus *Coccidioides immitis*, which is found in the soil of certain semi-arid areas of North and South America. This outbreak was associated with exposure to increased levels of airborne dust subsequent to landslides in the aftermath of the earthquake [47].

Plague may become a problem for refugees or returnees in endemic areas because of overcrowding and poor hygienic conditions (if human fleas are playing a role), or when they settle in or enter into contact with areas of wild rodent infection. Cases of plague have been suspected in refugee populations in Malawi and Mozambique [48, 49].

Vector-Mediated Skin Diseases

Natural disasters, particularly meteorological events such as cyclones, hurricanes, and flooding, can affect vector breeding sites and vectorborne disease transmission. While initial flooding may wash away existing mosquito breeding sites, standing water caused by heavy rainfall or overflow of rivers can create new breeding sites. This can result in an increase of the vector population and potential for disease transmission, depending on the local mosquito vector species and its preferred habitat. The crowding of infected and susceptible hosts, a weakened public health infrastructure, and interruptions of ongoing control programs are all risk factors for vectorborne disease transmission [50]. Refugees living in crowded, temporary settings, currently numbering more than 50 million worldwide, are subject to explosive outbreaks of communicable disease of low endemicity, such as cutaneous leishmaniasis (CL) [27].

Leishmaniasis is a neglected tropical disease, endemic in many worldwide foci including the Middle East. Both cutaneous and visceral forms are reported from the region ranging from the Levant to Afghanistan. Several outbreaks have occurred in the Middle East over the past decades, mostly related to war-associated population migration. Refugees, armed forces, and multinational contractors are particularly at risk of acquiring the disease. With the start of the Syrian war, the frequency and magnitude of these outbreaks increased alarmingly [51]. In fact, the recent resurgence of CL in the southern and southeastern Anatolia region in Turkey is a result of the influx of immigrants from neighboring countries where CL incidence is higher. Because of the civil war in Syria, immigrants to this region in the last 3 years have begun to present more frequently with this disease [52].

The sudden increase in leishmaniasis cases in Lebanon in 2013 is also attributed to the increasing numbers and wide distribution of Syrian refugees in Lebanon [51]. There has been an upsurge in leishmaniasis research, especially as new foci are exposed and the need to protect the naive populations moving into endemic areas becomes a public health priority [53].

Malnutrition and Vitamin Deficiencies

Commonly, economic crises and political insecurity (especially war) create and aggravate food insecurity. During these situations, populations try to cope with damaged infrastructure, and looted crops and homes. In conflict situations, individuals or groups may aim to have control over food (of others) in order to manipulate civil populations and feed the militia. This results in a reduction of food availability and accessibility, and an increase in population movements. Armed conflicts can also significantly deteriorate the baseline nutritional status of children and their families; more serious and devastating effects are seen when the conflict persists over time. Natural disasters are rarely the only cause of food insecurity, which can be prompted by a

gradual deterioration of food access caused by prolonged or repeated droughts, flooding, large livestock epidemics, and/or economic crisis. As food insecurity progresses to famine there is an increased prevalence of malnutrition, resulting in increased mortality [38]. The analysis of data collected in 42 camps in Asia and Africa indicates a clear association between the prevalence of malnutrition and high mortality rates in refugee camps in the emergency phase [54]. Protein-energy malnutrition (PEM) is known to be a major contributory cause of death in refugee populations, mostly because malnutrition increases vulnerability to diseases and thus its severity, especially in regard to measles [54, 55].

The term PEM applies to a group of related disorders that include marasmus, kwashiorkor, and intermediate states of marasmus-kwashiorkor. The most evident clinical feature in marasmus is severe wasting with loss of muscle and fat mass. Patients are extremely emaciated with thin, flaccid skin and prominent scapulae, spine, and ribs. Loss of facial fat results in the characteristic elderly appearance of affected children. Clinical features in kwashiorkor include bilateral pitting edema of the lower legs and feet; generalized edema in advanced cases (face, hands, arms, trunk); loss of muscle and fat mass (which can be masked by edema); skin lesions (atrophy, patches of erythema, hypo- or hyperpigmentation, desquamation, exudative lesions that resemble burns, fragile skin prone to ulceration and infection); and changes in hair color (lightening or becoming reddish) and texture (dry, thin, brittle, sparse hair that can be pulled out easily and without pain) [56] (Figs. 51.2 and 51.3).

In addition to PEM, micronutrient deficiencies play a key role in nutrition-related morbidity and mortality [54, 55]. Many scurvy outbreaks have occurred in displaced and famine-affected populations, primarily because of inadequate vitamin C in rations. Fortification of foods with vitamin C is problematic because vitamin C cannot be stored in the body. The best solution is to provide vitamin C through a variety of fresh foods, either by including them in the general ration or by promoting access to local markets [44]. Scurvy outbreaks are likely to occur in arid areas, especially during the dry season, when

Fig. 51.2 A malnourished boy admitted to the IPD because of exudative skin lesions related to the malnutrition condition. MSF clinic in Doro refugee camp, South Sudan, 2013

refugees have been settled for a few months and have only limited access to fresh fruits, vegetables, or milk on the local market [57, 58].

Pellagra (deficiency in niacin or vitamin B3) is endemic where people eat a maize-based diet with little protein-rich food. Pellagra outbreaks can occur in refugee and displaced populations dependent on food rations based on maize and containing insufficient quantities of groundnuts [59]. A large-scale pellagra outbreak occurred among Mozambican refugees in Malawi (1989 and 1990) [60, 61], and pellagra cases have been reported in several refugee camps (Zimbabwe, Angola, and Nepal in 1993) [62]. Outbreaks of other vitamin B deficiencies have been documented in refugee populations: vitamin B2 in Afghanistan in 1994, and vitamin B5 (nutritional neuropathy) in Afghanistan in 1993 [59]. As these deficiencies are often found in association, the clinical picture may cover a large spectrum of signs: neuropathy with burning feet syndrome, glossitis, conjunctivitis, and angular stomatitis, among others. However, one of these symptoms

Fig. 51.3 A severely malnourished girl with kwashiorkor admitted to the intensive therapeutic food center for nutritional therapy. Generalized edema and secondary bacterial skin infection are seen. MSF clinic in Doro refugee camp, South Sudan, 2013

will generally be dominant. These outbreaks are probably underreported because the symptoms are nonspecific and may be masked by other deficiencies, or the clinical signs are assumed to be due to other causes. The main recommendation in regard to these deficiencies is to be aware that a sudden increase in the number of cases of stomatitis, conjunctivitis, glossitis, burning feet syndrome, and other signs of neuropathy could be linked to vitamin B deficiencies [59].

Future Perspectives

The front-line field operators in emergency situations are usually volunteers, working for a range of different international nongovernmental organizations, and local health professionals, who frequently have diverse competencies, experience, and background. For instance, at the same emergency operation, European and American doctors share routine tasks with Asian and African ones.

In remote areas, the lack of medical human resources besides the lack of coordination with experts and reference centers make the medical assistance challenging. The nonadoption of standard guidelines and training can aggravate the mishandling of clinical cases. Furthermore, the quality of medical care delivered by international organizations is heterogeneous, even in the same country or population. Humanitarian actors should work closely by using standardized clinical guidelines, mostly focused in nutrition support, public health surveillance, immunization, communicable disease control, epidemic management, and maternal and child healthcare. Such skills are specific to emergencies and are not necessarily acquired in the average medical or nursing school. Once those requirements are achieved, most probably the management of particular conditions such as skin diseases in the field could be ameliorated through specific training and experience sharing. Nevertheless, humanitarian actors need to function effectively in different cultural contexts and, often, in hostile and dangerous environments.

Considering that geographic and political barriers still challenge the access of humanitarian health workers in the field, it is opportune to develop and access alternative tools of communication and technology, such as telemedicine. In response to medical emergencies and disasters, telemedicine has been used to deliver medical care in remote locations. Medical doctors from all over the world can be connected to share knowledge and personal experience, so that an African doctor can contribute by sharing his experiences in managing malnutrition; in turn, a European doctor can provide information on treating severe burns. In areas with no access to dermatologic care because of distance or simple manpower, teledermatology seems like an ideal solution to reach the underserved. However, many factors such as cost, lack of access to modern communication, and underdeveloped infrastructure serve as major obstacles to its widespread use.

The role of teledermatology in emergency care has been sustained by the action of private and nonprofit initiatives that assist poor, sick, and disabled people in the developing world through consultation services, allowing for the provision of access to expert medical advice from consul-

tants around the world to disaster and postconflict areas, including Afghanistan, Iraq, and Nepal. Services are provided in many specialty areas including dermatology, with high-resolution digital cameras and tripods, and training of the local medical staff in the proper use of the equipment, allowing remote hospitals in developing countries to receive assistance free of charge [63]. Natural and man-made disasters both require near-term and long-term interventions to reduce morbidity and mortality among the surviving victims. Information technology and modern portable communication devices should be incorporated in disaster preparedness and recovery training and operations [64]. Future efforts need to focus on expanding the outreach of these existing humanitarian teledermatology networks, and there is a need to invest in inexpensive technology and strategies to sustain programs in developing countries and remote areas that suffer from a high burden of disease with limited resources.

According to the international experience of providing dermatologic services and taking into account that natural disasters and armed conflicts are a global issue, it is reasonable to establish an international coordination center of emergency dermatology, which will unite representatives of national dermatologic societies and other public organizations and nonprofit foundations. The aims are to provide emergency and routine advisory dermatologic care to the affected populations in disaster and conflict areas, to ensure the appropriate care in specialized medical institutions with evacuation of patients when indicated, to encourage interdisciplinary cooperation, and to establish an efficient use of the medical and human resources available.

Glossary

Airborne   Transported by air.
Case-fatality rates (CFR)   A measure of the severity of a disease, defined as the proportion of reported cases of a specified disease or condition which are fatal within a specified time.
Foodborne   (Of a disease) carried by or transmitted through contaminated food.

Glossitis   Inflammation of the tongue. Glossitis is often caused by nutritional deficiencies and may be painless or cause discomfort
Médecins Sans Frontières (MSF) or Doctors Without Borders   An international, independent, medical humanitarian organization that delivers emergency aid to people affected by armed conflict, epidemics, natural disasters, and exclusion from healthcare.
Vectorborne   (Of a disease) transmitted by the bite of infected arthropod species, such as mosquitoes, ticks, triatomine bugs, sandflies, and blackflies.
Waterborne   (Of a disease) transported or transmitted by water.
Xerophthalmia   Abnormal dryness and thickening of the conjunctiva and cornea caused by vitamin A deficiency

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Vaccines and the Prevention of Dermatologic Diseases

52

Giancarlo Bessa

Key Points
- The impact of vaccines in the control of various infectious diseases is a very relevant topic in public health
- The HPV vaccines are most effective when administered before the onset of sexual activity
- A major obstacle to widespread use of zoster vaccine is the high cost
- Despite its variable protective efficacy, BCG is the best available vaccine for the prevention of leprosy

Introduction

Immunization is the process of inducing immunity through the administration of antigens or antibodies. Active immunization is the situation whereby a person is stimulated to produce antibodies by antigen administration. Sometimes the protection achieved is permanent and occasionally is partial, requiring reinforcements. Passive immunization corresponds to the administration of exogenously produced antibodies for temporary protection [1]. Classification of vaccines according to their composition is provided in Table 52.1.

Table 52.1 Classification of vaccines according to their composition [1]

Toxoid vaccine	Composed by a bacterial toxin modified to become nontoxic while retaining the ability to stimulate antibody formation
Attenuated vaccine	Vaccine that includes live bacteria or viruses that have lost virulence after growing under adverse conditions, but retain the ability to replicate and produce immunity without causing disease
Inactivated vaccine	Vaccine that contains killed bacteria or viruses, which are inactivated by chemical or physical procedures. This type of vaccine generally requires multiple doses for primary immunization and posterior booster doses to maintain adequate serum concentrations of antibodies
Subunit vaccines	The infectious organism is processed to purify those components to be included in the vaccine. These vaccines are categorized in three groups: protein-based, polysaccharide, and conjugate vaccines
Combined vaccines	Vaccines that comprise different antigens from several infectious agents in the same presentation, applied in a single administration. The necessary condition for combined vaccines is the preservation of the efficacy of the various components without increasing adverse reactions

Vaccination is considered the most efficient and cost-effective strategy to prevent infectious

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diseases [2]. The impact of vaccines in the control of various infectious diseases is a very relevant topic in public health. Mass vaccination campaigns promoted in the past century led to drastic reductions in the incidence or even eradication of major childhood infectious diseases including smallpox, polio, tetanus, diphtheria, pertussis, measles, rubella, mumps, and *Haemophilus influenzae* type b–related diseases [3]. Although they are fundamental in childhood, specific vaccination schedules also exist for adolescents, adults, the elderly, and select groups such as immunocompromised persons, health professionals, and travelers.

Available vaccines are generally well tolerated. Some precautions are necessary in conditions that can increase the risk of adverse reactions or compromise the ability of the vaccine to produce immunity. Common precautions are moderate to severe acute illness, mild or moderate allergies to vaccine components, pregnancy, anticoagulation, and immunosuppression. Previous anaphylactic reaction to a vaccine is a contraindication for application of subsequent doses of the product [4]. Vaccines with live components generally should not be given to pregnant women and immunocompromised individuals. The use of immunosuppressants, corticosteroids at high doses, immunoglobulins, and blood products is a temporary contraindication to the application of certain live attenuated vaccines. Anticoagulated individuals should avoid intramuscular administration. Subcutaneous or intradermal routes may be used if previously authorized by the manufacturer [1, 4]. Antipyretics such as acetaminophen reduce the incidence of vaccine-related febrile reactions, although they should not be routinely used because they can reduce the antigenic response [5].

State of the Art

Routine vaccination schedules can protect the population from infectious diseases both individually and through induction of herd immunity. Herd immunity refers to indirect immunity, when the vaccination of a portion of the population (the "herd") provides protection to unvaccinated individuals, through the theory that the chain of infection is interrupted when large numbers of the population are immune. Herd immunity requires vaccination rates to be high [3].

The World Health Organization (WHO) periodically reviews the medical literature on immunizations and publishes Position Papers providing global vaccine and immunization recommendations for diseases that have an international public health impact [6]. These recommendations are designed for immunization managers worldwide and are summarized in tables (Table 52.2). The WHO emphasizes that the recommendations are not intended for direct use by health workers; rather, their purpose is to aid technical decisions with respect to national vaccination schedules.

Vaccines are available for prevention of various infectious diseases. This chapter focuses on discussing the vaccines of dermatologic interest.

Vaccines Against HPV

The family of human papillomavirus (HPV) comprises more than 200 genotypes, approximately 40 of which can induce infections in the anogenital area [57]. Visible anogenital warts (condylomata acuminata) are commonly induced by HPV-6, -11, -42, -44, -51, -55, and -69 strains. Subtypes HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, and -68 are known for the potential of inducing malignant lesions, notably invasive cervical carcinomas in women. Mixed infections (presence of more than one oncogenic HPV genotype within a lesion), are not uncommon [57, 58].

Most HPV infections are asymptomatic and clear up within a few years [59]. Persistence of infection by an oncogenic HPV subtype in female genital tract was associated with higher risk of invasive cervical cancer [60].

The reason for failure of the immune system in otherwise healthy individuals to clear HPV infections for months or years remains incompletely understood. Some possible mechanisms are poor antigen presentation and effector

Table 52.2 WHO recommended routine immunizations for all immunization programs [7]

Vaccine	Children	Adolescents	Adults
BCG	One dose		
Hepatitis B	Three to four doses	Three doses (for high-risk groups if not previously immunized)	
Polio	Three to four doses (at least one dose of IPV) with DTP		
DTP	Three doses		
	Booster (DTP) 1–6 years of age	Booster (Td)	Booster (Td) in early adulthood or pregnancy
Haemophilus influenzae type b	Three doses, with DTP		
	OR		
	Two or three doses, with booster at least 6 months after last dose		
Pneumococcal (conjugate)	Three doses, with DTP		
	OR		
	Two doses before 6 months of age, plus booster dose at 9–15 months of age		
Rotavirus	Rotarix: two doses with DTP		
	RotaTeq: three doses with DTP		
Measles	Two doses		
Rubella	One dose	One dose (adolescent girls and/or child bearing aged women if not previously vaccinated)	
HPV		Two doses (females)	

Adapted from: WHO recommendations for routine immunization – summary tables. Available from: http://www.who.int/immunization/policy/immunization_tables/en

response, or virally induced local immunosuppression resulting in the development of tolerance [61].

The HPV vaccination rationale is to avoid genital infections and its associated morbidity. HPV is implicated in virtually all invasive cervical cancers (and precancerous lesions) and genital warts [62]. Although screening programs have significantly reduced the incidence of cervical cancer, it remains a considerable public health burden [59]. HPV infection is also the cause of a proportion of cancers of the anus, the oropharynx, the vulva and vagina, and of the penis, although the incidence rates for these cancers are much lower than for cervical cancer [64]. The prevalence of HPV infection is higher among teenagers and in the early twenties, decreasing with advancing age [63].

The WHO position paper [10] recommends that HPV vaccines should be included in national immunization programs if prevention of cervical cancer and other HPV-related diseases constitutes a local public health priority and vaccine introduction is feasible, considering sustained financing and cost-effectiveness. The priority target group for HPV vaccination is girls aged 9–13 years, prior to becoming sexually active, because HPV vaccines are most efficacious in those who have not previously been exposed to the virus. There is no specific recommendation for any formulation of the vaccine. The document also highlights the need for a comprehensive strategy that should include education about reducing risky sexual behaviors, training of health workers, and maintenance or improvement of programs of screening, diagnosis, and treatment of precancerous lesions and cancer.

Formulations

Three prophylactic vaccines are currently available: a bivalent vaccine that targets HPV types 16 and 18; a quadrivalent vaccine that targets HPV types 6, 11, 16, and 18; and more recently a 9-valent vaccine that targets HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The three vaccines were developed using recombinant technology and are prepared from purified L1 structural proteins. Neither of these vaccines contains live biological products or viral DNA, and are therefore noninfectious. They are administered as an intramuscular injection [65].

Schedules

The HPV vaccines are most effective when administered before the onset of sexual activity, i.e., before first exposure to HPV infection. However, sexually active individuals can be vaccinated according to recommendations based on age. The USA Advisory Committee on Immunization Practices (ACIP) recommends routine HPV vaccination (bivalent, quadrivalent, or 9-valent) for women at 11 or 12 years old, and for those aged 13–26 years who have not been previously vaccinated [2]. ACIP also recommends routine use of quadrivalent or 9-valent HPV vaccine for men at 11 or 12 years old and those aged 13–21 years if they have not yet been vaccinated. Men who have sex with men (MSM) and those immunocompromised, in particular, could benefit from vaccination to prevent condyloma and anal cancer [66, 67]. This is why ACIP recommends routine vaccination for this group through age 26 (if not previously vaccinated). Other men aged 22–26 years can be vaccinated but are not considered to be a priority for inclusion in routine vaccination schedules [20].

The WHO suggests that vaccination strategies should initially prioritize high coverage in the WHO-recommended primary target population of young females of 9 through 13 years of age. Vaccination of other populations is recommended only if this is feasible, affordable, and cost effective, and does not divert resources from vaccinating the primary target population or from cervical cancer screening programs [10].

HPV vaccines were originally licensed and marketed using a three-dose immunization schedule. The second dose can be administered in 1–2 months after the first, and the third dose is administered 6 months after the first (at least 24 weeks after first dose) [20]. A systematic review of quadrivalent and bivalent vaccines indicated that a two-dose (0 and 6 months) schedule in girls aged 9–14 years were noninferior to the three-dose schedule in terms of immunogenicity [29]. Based on this the WHO recommends administration of quadrivalent HPV vaccine for girls and boys aged 9–13 years according to the two-dose schedule, and the same for bivalent HPV vaccine for girls aged 9–14 years. The nonavalent (9-valent) vaccine was not considered in the current WHO position paper (2014) because it was under regulatory assessment at that time [10].

Pre- or postvaccination serology or HPV DNA testing are not recommended because prevaccinal serostatus is not a criterion for HPV vaccine candidacy, and there is no evidence that the measurement of postvaccination antibody titers is useful for determining immunity [73].

Clinical Evidence

Quadrivalent vaccine efficacy was assessed in two large randomized trials that enrolled more than 17,000 young women [68, 69]. In the major study, the efficacy of the vaccine for preventing the composite outcome of cervical intraepithelial neoplasia grade 2 or 3, adenocarcinoma in situ, and invasive carcinoma of the cervix due to HPV types included in the vaccine, among HPV-naive women, was 97–100%. In the overall population of study participants (intention-to-treat analysis), the efficacy of the vaccine was significantly lower (approximately 44%), which was associated with the fact that the most of subjects were sexually active and many had previous contact with vaccine HPV types [68]. In the other study, the efficacy for preventing external anogenital and vaginal lesions due to vaccine-type HPV, among HPV-naive women, was 100%. In the intention-to-treat analysis, the efficacy was 73% for HPV types included in the vaccine and 34% for lesions associated with any HPV type [69].

Quadrivalent vaccine efficacy was also evaluated in a trial of 4065 men aged 16–26 years (3463 heterosexual and 602 MSM with ≤5 sexual partners) [66]. Among HPV-naive males, the efficacy for preventing incidence of external genital lesions (primary endpoint) due to HPV types included in the vaccine was 90%. Efficacy against persistence of HPV infection (secondary endpoint) was 86%. In the overall population of study participants (intention-to-treat analysis), the efficacy was 66% for preventing external genital lesions and 48% for preventing persistent HPV infection. The efficacy of the HPV quadrivalent vaccine in preventing anal intraepithelial neoplasia secondary to vaccine-types HPV was assessed in the subpopulation of 602 MSM of the study [67]. The vaccine efficacy for this group was 78% among HPV-naive men and 50% in the overall MSM population.

Bivalent vaccine efficacy was assessed in two large randomized trials [70, 76]. The major study enrolled more than 18,000 women aged 15–25 years [70]. The efficacy of the vaccine for preventing the composite outcome of cervical intraepithelial neoplasia grade 2 or 3, adenocarcinoma in situ, and invasive carcinoma of the cervix due to HPV types included in the vaccine, among HPV-naive women, was 93%. In intention-to-treat analysis (overall population of study), the efficacy was 53%. Bivalent vaccine efficacy in older women was evaluated in a trial of 5752 women ≥25 years [71]. Among HPV-naive females, the efficacy for preventing the composite outcome (persistent cervical infection for 6 months or cervical intraepithelial neoplasia grade 1 or more severe disease, both associated with vaccine-type HPV) was 81%. For the overall participants in the study, the efficacy was 44%.

The nonavalent HPV vaccine efficacy was assessed in a large trial of 14,215 women aged 16–26 years who were randomized to receive the 9-valent or the quadrivalent HPV vaccine [72]. The composite outcome included cervical intraepithelial neoplasia grade 2 or more severe disease, vulvar intraepithelial neoplasia grade 2 or 3, and vaginal intraepithelial neoplasia grade 2 or 3, associated with HPV types 31, 33, 45, 52, and 58. The efficacy of the vaccine among HPV-naive women was 97%. For the overall participants the rate of high-grade cervical, vulvar, or vaginal disease irrespective of HPV type was the same in both vaccine groups (14.0 per 1000 person-years).

Long-term data about bivalent and quadrivalent vaccines reported persistent serum antibody levels and protection against HPV infection up to 9 years after vaccination [79, 80].

Special Populations

Cases of pregnant women inadvertently enrolled in phase III clinical trials were reported in the HPV vaccine groups, and abnormal pregnancy outcomes following administration do not appear to be associated with vaccination [68]. However, vaccination during pregnancy is not recommended because of limited data on safety. Lactating mothers may be vaccinated [73].

The HPV vaccine can also be administered to subjects with a history of genital warts or abnormal Papanicolaou test or positive HPV DNA test result, because immunization can still prevent infection by vaccine-type HPV that was not already acquired [73].

HPV vaccines do not have live virus particles and can be administered to individuals with immunosuppression due to infections (including human immunodeficiency virus (HIV) infection), illness, or medications. The vaccine is recommended for immunocompromised patients through age 26 years [73]. There is evidence of immunogenicity and safety of quadrivalent vaccine in HIV-infected patients [74, 75]. However, data on effectiveness are not yet available.

Safety

HPV vaccines appear to have satisfactory safety profile in the context of clinical trials [66, 68, 72]. Local reactions, particularly pain, occur at relatively high rates, having been reported in up to 80% of immunized individuals for both bivalent and quadrivalent vaccines, but this is usually of short duration and resolves spontaneously. Systemic reactions have generally been mild and self-limited [77]. Fever occurred about 2% more frequently in vaccine groups. Other minor

systemic adverse events such as headache, dizziness, myalgia, arthralgia, and gastrointestinal symptoms were reported, but with <0.5% difference in the vaccinated group [10]. Postvaccination syncope has occurred, but can be avoided with appropriate care [77]. Serious vaccine-attributable adverse events, such as anaphylaxis, are rare (0.1 per 100,000 doses of quadrivalent vaccine in the United States) [78].

Vaccines Against Varicella Zoster

The causal agent of both varicella (chickenpox) and herpes zoster (shingles) is the varicella zoster virus (VZV), a highly prevalent virus affecting the human race. Only one serotype is known, and in nature VZV infects only humans [15]. The majority of primary infections occur as varicella in early childhood, which is generally a benign, self-limiting disease in immunocompetent children. Varicella infection usually confers immunity for life. Second attacks of varicella are rare in immunocompetent persons but have been documented. After resolution of varicella VZV remains latent, with occasional reactivation as the herpes zoster (HZ) disease [8].

Varicella

Vaccines against both varicella and HZ are based on live attenuated VZV (Oka strain) but at different virus titers. Although Oka strain is clinically attenuated, it can cause mild varicella, establish latency, and, theoretically, reactivate to cause HZ [14]. The United States introduced universal varicella vaccination in 1996, and Australia in 2000. Both countries have subsequently experienced a substantial decrease in disease burden [17, 18].

The varicella vaccination rationale is to avoid associated morbidity (which may be mediated either by VZV or secondary bacterial infection) such as encephalitis, cerebellar ataxia, pneumonia, sepsis, and the congenital varicella syndrome [9]. Although complications are more frequent at the extremes of age and in individuals with underlying chronic disease, most cases of complications arise in previously healthy individuals [16]. Rarely these complications may result in

death, especially among neonates and immunocompromised persons [13]. The WHO position paper [9] considers that varicella vaccination is of value for public health by lowering morbidity and mortality arising from VZV, particularly in vulnerable population groups. It suggests that authorities should consider introducing varicella vaccination in the routine childhood immunization programs in countries where varicella is a relatively important public health problem and where the resources are sufficient to ensure high (85–90%) and sustained vaccine coverage. Additionally the vaccine may be offered in any country to individual adolescents and adults without a history of varicella, mainly with a high average age (≥15 years) of acquisition of infection, indicating a high proportion of susceptible persons in the population.

Formulations

The varicella vaccine is available either as a monovalent (varicella only) or in combination with measles, mumps, and rubella (MMR) vaccine, and is administered subcutaneously [19]. All vaccines are licensed for use in persons aged ≥12 months; one monovalent and two combined vaccines are licensed for use from 9 months of age in some countries. There is an acceptable variability in the virus concentrations among different varicella vaccines, and currently licensed vaccine content varies from 1000 to 17,000 plaque-forming units [9].

Schedules

The WHO suggests that the first dose be administered at age 12–18 months. Each country should decide on the number of doses of the schedule, depending on the goal of the vaccination program. One dose can reduce mortality and severe morbidity from varicella but does not prevent limited virus circulation and outbreaks. Two doses have higher effectiveness and are recommended for countries where the programmatic goal includes the reduction of the number of cases and outbreaks. The second dose (for countries with a two-dose schedule) should be administered as recommended by the manufacturer, ranging from 4 weeks to 3 months after the first

dose [9]. The ACIP recommends routine two-dose varicella vaccination for children, with the first dose administered at 12–15 months of age and the second dose at age 4–6 years [19]. It is also recommended for adolescents ≥13 years and adults without evidence of immunity, which requires a two-dose schedule separated by 4–8 weeks [20]. Some European countries, such as the United Kingdom and France, do not recommend universal immunization [41]. It is particularly important to immunize susceptible individuals who have close contact with immunocompromised patients at high risk of severe disease, such as healthcare workers and household contacts [9, 19, 20].

Since the routine schedule for varicella vaccine generally is the same as that for MMR vaccine, either monovalent or combination MMRV vaccines can be used, taking into consideration the safety and effectiveness profiles, including a higher risk for febrile seizures after the first dose (when administered at 12–18 months) but not after the second dose [9]. Based on this the ACIP and the American Academy of Pediatrics suggest that the first doses of varicella and MMR vaccines should be administered at different sites for children 12 through 47 months of age (even if given at the same visit). The first doses for children 48 months through 12 years of age and the second doses for children 15 months through 12 years of age can be administered as MMRV vaccine. Adolescents and adults should receive single-antigen varicella vaccine [21, 22].

Pre- or postvaccination serology is not recommended because available commercial tests do not detect low levels of antibody and cannot reliably exclude immunity in exposed or vaccinated individuals [31].

Clinical Evidence

Pre- and Postlicensure studies have demonstrated that the vaccine against VZV is effective in preventing varicella, decreases disease severity in breakthrough cases, minimizes the risk of transmission, and reduces varicella-associated health care utilization [23–27]. Indirect protection of persons outside the vaccinated cohorts was also documented [28].

A systematic review [29], provided by the WHO Strategic Advisory Group of Experts (SAGE), of 40 studies about varicella vaccine effectiveness, showed that a single dose of varicella vaccine had an approximate effectiveness in preventing 80% of varicella cases of any severity; 95% of moderate disease; and 99% of severe cases. Two doses were demonstrated to be more effective, yielding a mean effectiveness of 93% against varicella of any severity.

The strategy of including the vaccine in routine immunization at 15–18 months of age seems to be better than vaccinating susceptible adolescents [42].

Contraindications and Special Populations

Varicella vaccine is contraindicated in pregnant women (pregnancy should be delayed for 4 weeks after vaccination) and in persons with a history of severe allergic reactions to a previous dose of varicella vaccine or a component of it [9, 19]. Breastfeeding is not a contraindication to administration. Varicella vaccine is usually contraindicated in the context of congenital or acquired immune deficiencies [32]. However, varicella vaccination (two doses) may be considered in these groups:

- Clinically stable HIV-infected children or adults without severe immunosuppression (CD4$^+$ T-cell levels ≥15% or ≥200 cells/μL), including those receiving highly active antiretroviral therapy (HAART), may receive single-antigen varicella vaccine [9, 20, 30].
- Children with leukemia in remission and patients with certain solid tumors who have successfully completed chemotherapy and are unlikely to relapse (administered at least 3 months after all chemotherapy has been completed) [9, 33]
- Isolated B-lymphocyte (humoral) deficiencies are not a contraindication to single-antigen varicella vaccine [9]
- Low-dose systemic glucocorticoid therapy (prednisone ≤20 mg per day or ≤2 mg/kg per day in children who weigh <10 kg, or equivalent) is not a contraindication to varicella vaccine. However, the vaccine should not be

administered in persons receiving higher doses of prednisone; immunosuppressive agents, such as those given to patients who have undergone solid organ or hematopoietic stem cell transplant; and during treatment with tumor necrosis factor α inhibitors and other biological agents for autoimmune conditions [32].

Postexposure Prophylaxis

Small trials suggest that vaccination of children within 3 days after an exposure to VZV decreases the risk of infection (23% versus 78%) and the severity of disease. The efficacy of postexposure prophylaxis in adolescents or adults remains uncertain [35].

Safety

It is advisable to delay vaccination in persons who have recently received immune globulin, blood products, or antiviral therapy, because of the potential inhibition of the immune response. The vaccine manufacturer also recommends that salicylates be avoided for at least 6 weeks after VZV vaccine [19].

Evidence on the safety of varicella vaccines concludes that monovalent varicella vaccine is generally well tolerated [36]. Local reactions (tenderness and redness at the injection site and localized varicella-like rash) are the most common adverse event (up to 25% of children which received combined or monovalent varicella vaccine) [34]. Fever was reported in 15% of children [9]. The risk of a febrile seizure after separate injections of varicella vaccine and MMR is approximately 1 in 2500 [21]. Urticaria was rarely reported, mainly after receipt of varicella vaccine in combination with other vaccine (2.2/100,000 doses). Postlicensure data from the United States showed the incidence of serious adverse events to be 2.6/100,000 doses [36]. Review of evidence for severe adverse events associated with varicella vaccines supports causality for rare occurrences: disseminated cutaneous infection by vaccine strain virus; disseminated vaccine strain virus infection with internal organ involvement in individuals with immunodeficiencies; vaccine strain reactivation (HZ) with or without organ involvement; and anaphylaxis [9].

Varicella vaccination raised concerns about its impact on the incidence of HZ, either by a risk of vaccine-associated HZ in immunized individuals or by an increase in general population incidence of HZ due to a reduction of exogenous boosting of immunity by naturally circulating VZV [39]. None of these concerns were supported by evidence. The incidence of HZ in vaccinated children is approximately 14 cases per 100,000 person-years [40]. Long-term follow-up of a group of individuals who received varicella vaccine as healthy young adults found that the incidence of HZ was similar to historical data in the prevaccine era in the United States [37]. Also, if given in childhood the vaccine does not appear to affect the incidence of HZ in individuals older than 65 years in general population [38].

It should be noted that varicella vaccine is licensed only to protect against varicella disease; it is not indicated for protection against HZ disease.

Herpes Zoster

About 10–30% of people infected by VZV will develop an episode of HZ during their lifetime. HZ incidence is related to waning specific cell-mediated immunity and is particularly high in elderly and immunocompromised subjects [43]. The most frequent complication of HZ is postherpetic neuralgia (PHN), defined as a pain along the affected sensory nerves lasting more than 90 days after the healing of the rash, which has a high impact on patients' quality of life [44].

Zoster immunization rationale is to boost VZV-specific T-cell immune responses, preventing or attenuating HZ disease [45]. The first developed HZ vaccine contains the same VZV Oka strain used in varicella vaccine, but at a much higher dose [29]. Zoster vaccination can help to reduce the occurrence and severity of HZ or the risk of PHN [46]. Therefore, it might be an interesting option for introduction into national immunization programs. The WHO position paper [10] does not offer any specific recommendation concerning the routine use of HZ vaccine in public health. The reason is due to the unknown burden of HZ in most countries and insufficient data concerning the use and duration of protection

of HZ vaccine. However, countries with high demographic shift toward older ages may consider introducing routine HZ vaccination if they have an important burden of disease.

Formulations

HZ vaccine composed by a live attenuated virus is administered as a single 0.65-mL subcutaneous injection [29]. Recently an inactivated zoster vaccine composed by VZV glycoprotein E in combination with an adjuvant has been developed. This vaccine requires two doses for protection [47].

Schedule

Despite the US Food and Drug Administration (FDA) having licensed zoster vaccine for use in persons over 50 years of age, the ACIP recommends beginning vaccination at age 60 years [48], independently of patient's previous history of varicella or HZ disease. There are no studies about vaccination of patients who have received the varicella vaccine. The ACIP does not recommend zoster vaccination in such patients.

The manufacturer of the pneumococcal vaccine, indicated for a similar age group, recommends that the zoster vaccine should be administered separately by at least 4 weeks, because coadministration would reduce the immunogenicity of the zoster vaccine [49]. Despite this, to reduce the probability of low adherence to both vaccines the ACIP has recommended the administration of pneumococcal and HZ vaccine at same visit [48], based on findings of an observational study that did not find differences in incidence of HZ between both situations [49].

Clinical Evidence

A large placebo-controlled primary prevention clinical trial of the live attenuated zoster vaccine, including 38,546 immunocompetent adults aged 60 years and older, has demonstrated a significant reduction in the burden of illness due to both clinical HZ and PHN. Immunization reduced the incidence of HZ by 51% compared with placebo (1.6% versus 3.3%, respectively) and of PHN by 67% (0.1% versus 0.4%, respectively) [46].

The HZ vaccine reduces disability related to pain by two-thirds and the impact on quality of life by half [53]. Most of this reduction was attributed to the prevention of HZ infection.

A meta-analysis of eight randomized trials that included 52,269 individuals 60 years of age or older showed results similar to those of the original study [50].

The efficacy of the vaccine in the age group from 50 to 59 years of age was tested in another placebo-controlled trial which showed significant reduction in the incidence of HZ (2 per 1000 person-years versus 6.6 per 1000 person-year in the placebo group) [52].

A major obstacle to widespread use of zoster vaccine is the high cost. Multiple cost-effectiveness analyses have been performed. A systematic review of 14 cost-effectiveness studies of HZ vaccination [54] showed that duration of vaccine-induced protection affected the ratio considerably. In general, HZ immunization is cost-effective when the vaccine is administered between the age of 60 and 75 years and the duration of vaccine-induced protection is longer than 10 years. However, long-term follow-up of individuals from the major trial suggest that the efficacy of the zoster vaccine is somewhat reduced approximately 8 years after vaccination [51]. It is not known whether a second dose can preserve immunity conferred by the HZ vaccine.

The efficacy of two doses of the new inactivated zoster vaccine was evaluated in a placebo-controlled clinical trial including 15,411 individuals aged 50 years and older. The overall vaccine efficacy to prevent HZ disease was 97.2% without significant adverse effects reported [47]. This vaccine may be particularly helpful in immunocompromised individuals.

Contraindications and Special Populations

As varicella vaccine, the live attenuated zoster vaccine is contraindicated in pregnant women. Also, it should not be administered to persons with history of an anaphylactic reaction to gelatin or neomycin [48]. Zoster vaccine should be avoided the context of congenital or acquired immune deficiencies [9]. However, low-level immunosuppressive therapy, such as prednisone

≤20 mg per day or methotrexate ≤0.4 mg/kg/week, is not a contraindication for vaccination [32]. The indications of zoster vaccine in HIV-infected individuals are not yet established. It can be considered in those with CD4 counts >200 cells/μL who are aged 60 years or older [55]. Healthcare providers can consider vaccination of candidates for solid organ transplants prior to transplantation, although its efficacy in preventing HZ disease during immunosuppression therapy following transplantation is unknown [56].

Zoster vaccine is not indicated for the treatment of HZ disease or PHN.

Safety

Clinical trials as well as postlicensure studies of the live attenuated zoster vaccine demonstrated a good tolerability and safety profile [9]. In a large study the incidence of serious adverse events was <0.1% [52]. Immunized subjects reported more frequent (26–35%) reactions involving the site of injection (erythema, pain, tenderness, swelling, and pruritus). An HZ-like rash (usually mild) has been registered in 0.1% of immunized individuals [9]. Transmission of the vaccine virus has not been reported. One patient had an anaphylactic reaction on the day of vaccination [52].

Vaccines Against Herpes Simplex

There are no vaccines currently available for protection against infection with either HSV-1 or HSV-2. Clinical studies of herpes simplex virus type 2 (HSV-2) subunit vaccines containing glycoproteins showed that, overall, the vaccine was not efficacious [81–83].

BCG Vaccination Against Tuberculosis and Leprosy (Hanseniasis)

The Bacillus Calmette–Guérin (BCG) vaccine was produced by in vitro attenuation of a strain of *Mycobacterium bovis* in the early twentieth century and is one of the most widely used vaccines. The objective of vaccinating neonates and infants is for prevention of severe tuberculosis (TB) [84]. BCG vaccine has a documented protective effect against meningitis and disseminated TB in children [85]. Evidence about the protection of BCG vaccine against *Mycobacterium tuberculosis* primary infection has been scarce. Recently, the development of modern techniques allowed discrimination of recent *M. tuberculosis* infection from previous BCG vaccination or contact with most nontuberculous mycobacterial infections, which was not possible with the tuberculin skin test [86]. Based on this, a meta-analysis of 14 studies demonstrated that BCG protects against *M. tuberculosis* infection (overall efficacy of 19% among vaccinated children after exposure) as well as progression from infection to disease (efficacy of 58% among those infected) [87].

By blocking the progression of *M. tuberculosis* infection, BCG could, theoretically, confer protection over some forms of cutaneous TB. However, the role of BCG as a preventive measure against cutaneous TB is controversial. In some reports, BCG vaccination appeared to protect against disseminated disease [88] and also to be effective in adults against cutaneous TB (efficacy of 60.9%) [89]. Nevertheless, other studies did not find any difference between the vaccinated and the unvaccinated groups in preventing cutaneous TB [90, 91].

The cross-reactivity between BCG and *Mycobacterium leprae* has been exploited in attempts to induce immunity against leprosy (also known as hanseniasis). BCG started to be used for the prophylaxis of leprosy in the 1940s [92] and the presence of a BCG scar has been recognized as a protective factor for the disease [95]. However, the efficacy of BCG in preventing leprosy has varied widely in studies. Meta-analyses demonstrated an overall efficacy of 26–41% in experimental studies and 61% in observational studies [93, 94]. BCG is mostly known as a vaccine for prevention of TB but, curiously, studies that tested the efficacy of the same BCG vaccine for TB and leprosy in the same populations have shown BCG to be more effective against leprosy than against TB [103].

Because of BCG's efficacy against leprosy, Brazil has officially recommended two doses of

BCG to be administered to household contacts of leprosy cases, as a boost to routine BCG vaccination in newborns, when it is applied as a TB prophylactic vaccine [104]. This approach was evaluated in a cohort study of 5376 contacts of 1161 leprosy patients in Brazil [105], showing that the efficacy of BCG was 56% and was not substantially affected by previous BCG vaccination (50% with and 59% without a scar). Interestingly, the risk of tuberculoid leprosy was high during the initial months among those vaccinated with no scar [105]. Another study in Bangladesh also identified a high proportion of healthy contacts of leprosy patients who presented with paucibacillary leprosy within 12 weeks after receiving BCG vaccination (all 21 contacts who developed leprosy in this period) [106]. This can be attributed to the boosted cell-mediated immunity due to antigens in BCG, which may accelerate and modulate clinical manifestations in subjects infected with *M. leprae* before or immediately after BCG vaccination [105].

In addition to BCG, the vaccine potential of killed *M. leprae* has also been assessed in clinical trials, but in most studies, BCG plus *M. leprae* vaccine did not offer better protection against leprosy than BCG alone [96, 97].

Protective efficacy of BCG has been reported to decrease with time and is generally thought to last no more than 10–15 years [11]. In contrast to what occurs with vaccination for TB, for which studies indicate no substantial benefit of BCG revaccination, the evidence suggests that multiple BCG doses enhance protective efficacy against leprosy [97], although this has been questioned by some studies [98].

Formulations

All BCG vaccine used nowadays contains descendant strains from the original *M. bovis* isolate obtained by Calmette and Guérin. The manufactured vaccine is a lyophilized compound which, after reconstitution, contains both living and dead bacilli. The number of cultivable bacilli per dose and the biochemical composition of the vaccine vary considerably depending upon the strain and production method [11].

Schedule

The WHO recommends that a single dose of BCG vaccine should be given to all infants as soon as possible after birth in countries with a high burden of TB and also to infants and children at particular risk of TB exposure in otherwise low-endemic areas. BCG revaccination for TB is not supported [11]. BCG is also administered at birth in most countries with high rates of leprosy, a fact that generally coincides with the WHO recommendation for TB because both diseases are common in low-income countries.

To date, despite its variable protective efficacy, BCG is the best available vaccine for the prevention of leprosy [94]. Besides the dose administered at birth, the Brazilian Ministry of Health recommends two doses of BCG to be administered to household contacts of leprosy patients [104].

BCG vaccine application should be intradermal, preferably on the deltoid region of the arm. Newborns normally receive half the dose given to older children, because they have a higher risk of vaccine-induced suppurative lymphadenitis. BCG vaccine can be given simultaneously with other childhood vaccines [11].

BCG vaccination of adults is not normally recommended but may be considered for tuberculin-negative persons in close contact with cases of multidrug-resistant *M. tuberculosis* [11].

Contraindications and Special Populations

BCG vaccination is contraindicated for persons with impaired immunity (symptomatic HIV infection, known or suspected congenital immunodeficiency, leukemia, lymphoma or generalized malignant disease); for patients under immunosuppressive treatment (corticosteroids, alkylating agents, antimetabolites, radiation); and in pregnancy [11].

Neonates of known HIV-positive mothers are at risk of disseminated BCG disease if they have rapid development of immunodeficiency. Based on this, the WHO recommends that [12]:

- In infants born to women of unknown HIV status, benefits outweigh risks for BCG vaccination and they should be immunized
- In infants whose HIV infection status is unknown and do not demonstrate signs or symptoms suggestive of HIV infection, but who are born to known HIV-infected women, the benefits usually outweigh risks for BCG vaccination and they should be immunized after consideration of local factors (prevalence and potential exposure to TB; capacity to conduct follow-up of immunized children; capacity to perform early virologic infant diagnosis)
- In infants who are known to be infected with HIV, risks outweigh benefits for BCG vaccination and they should not be immunized
- In infants whose HIV infection status is unknown but who have signs or symptoms suggestive of HIV infection and who are born to HIV-infected mothers, risks usually outweigh benefits for BCG vaccination and they should not be immunized.

Safety

After 2–6 weeks of BCG vaccination a variable local reaction usually occurs (erythema, induration, tenderness, and ulceration), often followed by a small scar at the site of the injection.

Complications following BCG vaccination are rare. Fatal dissemination of BCG occurs almost exclusively in inadvertently immunized persons with severely compromised cellular immunity. Extensive ulceration and regional lymphadenitis sometimes occurs, but is also much more common in immunodeficient persons [11].

Specific complications caused by the BCG organism include lupus vulgaris at the vaccination site [99]. Case reports have also documented occurrence of scrofuloderma [100], papular tuberculids [101], and erythema induratum of Bazin [102] following vaccination. Antituberculous therapy is not necessary for these hypersensitivity reactions to *M. bovis* in immunocompetent patients.

Future Perspectives

Despite major advances in the field of vaccinology over the last decades, there are still possibilities for improvement. Vaccines are being developed both to prevent and to aid in the treatment of HSV-2 infection [107]. Multiple molecules are under study for the development of new vaccines against varicella and HZ. Complete prevention of both varicella and HZ is the only path that will lead to eradication of VZV, and future research should consider the reduction of VZV infection in the general population as a primary outcome [108].

Regarding HPV vaccines, it is important to generate more data on longer-term clinical efficiency and to define the duration of protection and cost-effectiveness after two-dose and three-dose schedules. Additional studies in low-income countries among healthy young females and among special populations (e.g., HIV-infected, malnourished, endemic malaria) would provide evidence of the impact of the vaccine in those populations [10].

Despite the positive impact of the WHO treatment campaign on the global prevalence of leprosy, there is still a need for further efforts toward eradication of the disease. These efforts should include an effective vaccine with potential for both prophylactic and therapeutic use. The development of an improved BCG vaccine, BCG booster, or alternative vaccine strain that could benefit control of both TB and leprosy is currently an important global research goal [109]. The most favored research strategies include recombinant modified BCG vaccines, attenuated strains of *Mycobacterium*, subunit vaccines, and DNA vaccines [11].

Glossary

Anaphylaxis A severe, potentially life-threatening allergic reaction. It can occur within seconds or minutes of exposure to an allergen. The flood of chemicals released by the immune system during anaphylaxis can lead the body into shock; the blood pressure

drops suddenly and the airways narrow, blocking normal breathing. Signs and symptoms of anaphylaxis include a rapid, weak pulse, a rash, and nausea and vomiting.

Genotypes   The genotype of an organism is the inherited map it carries within its genetic code. It is the part (DNA sequence) of the genetic makeup of a cell, and therefore of an organism or individual, which determines a specific characteristic (phenotype) of that cell/organism/individual.

Revaccination   The vaccination administered some time after an initial vaccination, especially to strengthen or renew immunity.

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Human Skin Bank

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Introduction

The skin bank has as its main functions the harvesting, processing, preservation, and supply of fine human skin allografts for burn treatment and polytrauma centers. Allograft skin acts as a temporary biological dressing to cover superficial and deep skin wounds. Its main clinical indication is for cases in which an extensive body surface area is compromised, impeding autograft transplantation [1].

Skin Harvesting

Skin can be donated from individuals who have died from brain death or cardiac arrest. As occurs for other organs and tissues regarding the possibility of donation, the donor's family is interviewed regarding the desire to donate organs and tissues, signing a consent form for donation.

Skin harvesting involves removing, with the aid of a dermatome or graft knife, thin slices of skin with thicknesses ranging from 0.8 to 1.0 mm [1].

In this process, slices are removed from the epidermis and a small part of the dermis, which are the most superficial layers of the skin [1].

The skin is removed from sites that can be "hidden" during the donor's funeral, such as thighs, legs, and back (Fig. 53.1) [1]. After removing the skin, the donor sites have a lighter color compared with the donor's skin tone; however, skin harvesting does not cause bleeding or harm to the donor's body (Fig. 53.2). Furthermore, the sites where the skin was removed are reconstituted with wound dressings, bandages, and plasters—the end of the skin-harvesting process. This minimizes possible loss of liquid following the removal of the body tissue barrier [1].

The whole process of skin harvesting must necessarily be performed in an operating room. To preserve tissue conditions and minimize potential microbial contamination, the skin-harvesting protocol is very similar to that of in vivo surgery. Clean rooms, antisepsis of hands and forearms, surgical scrubs, and use of sterile materials are part of the routines of skin harvesting [2].

Chronologically, the stages of skin harvesting are: (i) The Center of Notification, Procurement and Distribution of Organs informs the skin bank team about the donation process (donor data, such as clinical history and serology, cause of death, age, and place and time of skin harvesting). (ii) The skin bank team (plastic surgeon and biomedical) moves to the

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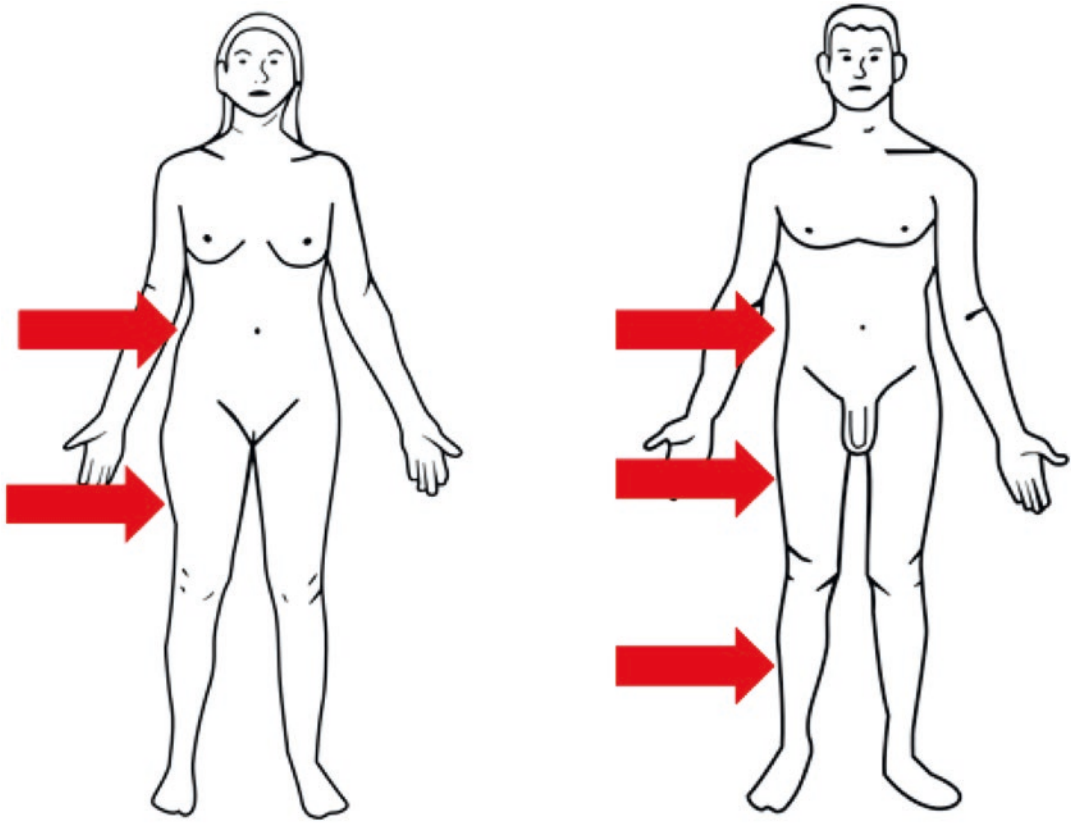
Fig. 53.1 Skin harvesting body sites

Fig. 53.2 Donor skin site before (*left*) and after (*right*) harvesting

hospital where the skin harvesting is to takes place and starts organizing the process. (iii) In the surgery center, the plastic surgeon responsible for the skin harvesting performs the physical examination of the donor body (evaluation of the skin quality). (iv) If the skin is viable for harvest, skin preparation is initiated: trichotomy and antisepsis of the donor sites. (v) The work area is prepared (placement of sterile fields) for the skin-harvesting process.

While in the operating room, the skin-harvesting process is initiated. The responsible biomedical technician performs a double wash of the skin slices with sterile saline solution. Soon after, microbiological screening of the tissue is performed by passing rayon swabs on the surface of each skin slice and small fragments are collected for subsequent placement in culture media (tryptone soya broth and thioglycolate). The skin is then packaged in bottles containing sterile 50% glycerol and transferred to a coolbox with periodic temperature control. The skin is taken to the tissue bank and kept under refrigeration (2–6 °C).

Skin Processing

Skin processing can be divided into three phases (Fig. 53.3). The first step is to wash the skin again with sterile saline and place it in more concentrated glycerol (85%). The second phase aims to "massage" the skin so that the free edges of the slice does not stick, as well as changing it over to a new 85% glycerol solution. The third and final stage consists in trimming the edges of the skin slices, packaging, and measurement of tissue in cm^2. In the case of skin contamination in the processing period, it is subjected to a specific antibiotic treatment in an attempt to eliminate the microorganisms, repeating as necessary after the three stages of processing.

Tissue Quality Control

After each stage of processing, collection of skin fragments is performed for microbiological analysis. The fragments are placed in culture media

that favor the growth and recovery of aerobic bacteria, anaerobic bacteria, and fungi that may be present in the tissue.

The tissue bank follows international guidelines [1], whereby the tissue acceptability criteria take into account the degree of pathogenicity of the organism and its potential to produce toxins. Thus, the presence of Gram-negative bacteria, *Staphylococcus aureus*, and fungi in tissue lead to its summary disposal. However, if the skin is colonized by bacteria of microbiota (coagulase-negative staphylococci) or environmental contaminants (such as those belonging to the genus *Bacillus*), it can be treated with antibiotics or physical methods such as irradiation, in order to leave sterile tissue [1].

Preservation Methods and Tissue Storage

Storage of the skin can be accomplished in two distinct forms, each of which has a direct relationship with the type of processing performed: glycerol under refrigeration at 2–6 °C or cryopreservation [3, 4].

The method using glycerol is cheaper and involves exposing the tissue to high concentrations of glycerol. Glycerol is a polyol which has as one of its properties the "sequestration" of water molecules, being characterized as a preserving solution. Accordingly, the tissue can be stored under refrigeration (4 ± 2 °C) for up to 2 years from the skin-harvesting date. On the other hand, in cryopreservation the skin associated with a cryopreservant is subjected to a slow and progressive decrease in temperature with subsequent storage at – 80 to −196 °C (in liquid nitrogen). The main advantage of this method is the longer storage time of 5 years [3, 4].

Tissue Release and Distribution

The release and distribution of allogeneic skin for clinical use only occurs after certification of tissue sterility.
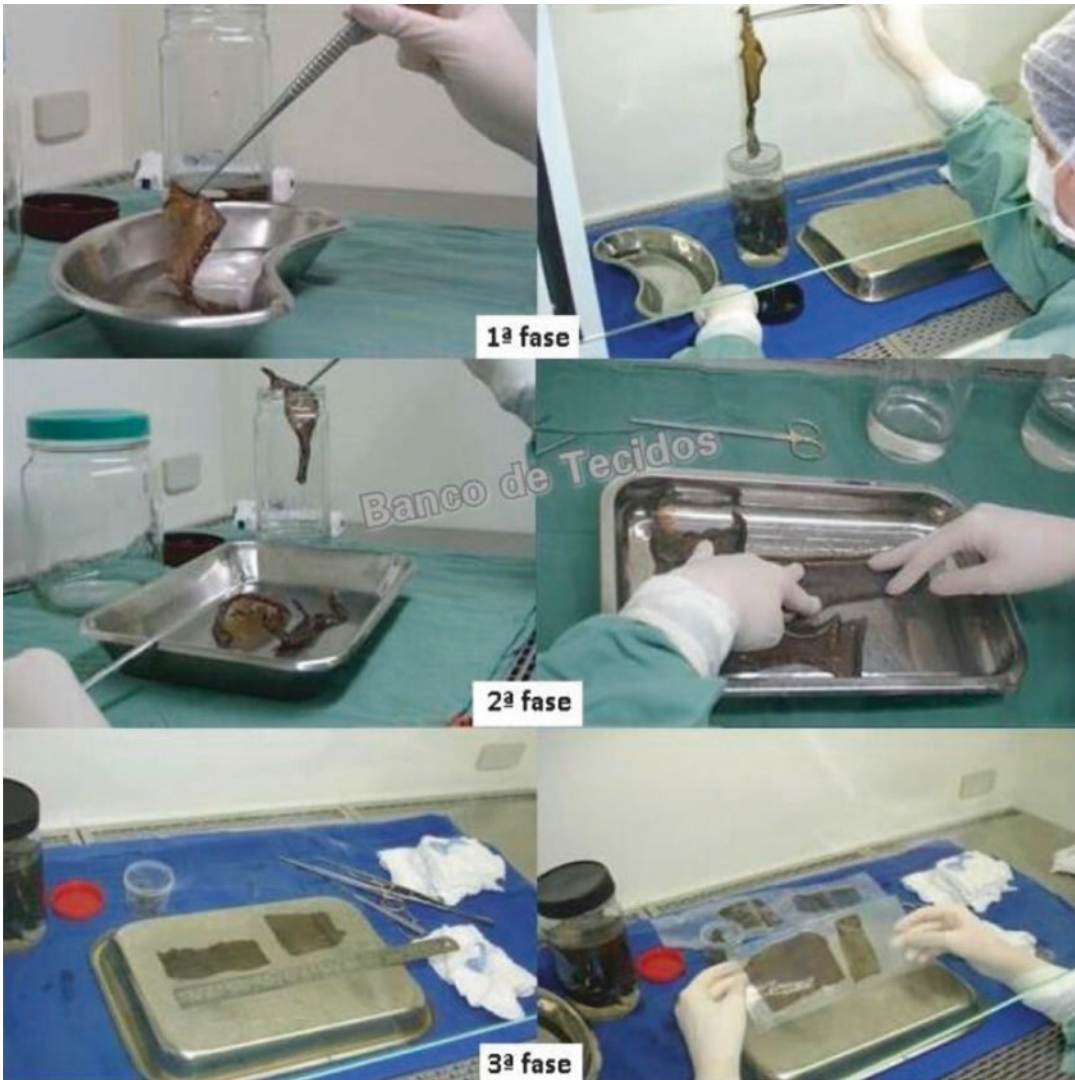
Fig. 53.3 Allogeneic skin processing steps (*1a fase* first step, *2a fase* second step, *3a fase* third step)

Tissue Release

The tissue is released after completing the three aforementioned processing steps in the absence of any microbial contaminant. Each pack of tissue is identified by a standard label which states: contact information of the tissue bank (address and telephone), the donor code, the type of processing (glycerol 85%), the expiration date (from the date of harvesting), the tissue area contained in each package (in cm^2), if there was contact with antibiotics during processing, the indication:

"Product Released for Use in Human," and the temperature of the tissue storage (4 ± 2 °C) [2].

Distribution of Tissue for Clinical Use

Tissue distribution is made to all burn treatment units of the country, being governed by the National Center of Transplants and Regional Center. The function of these regulators is to assess the skin request content, verify that both

the doctor and the transplantation hospital are properly registered in the National Center of Transplants, and issue an authorization for sending and carrying out the transplant.

The tissue bank separates from the stock of released tissue the amount of skin required and organizes its delivery to the center of transplantation. Shipping can be done by land or air according to the distance from the burns unit.

Sent along with the tissue are instructions for handling and use of allogeneic skin, as well as documents containing the record about the tissue, a "Consent Form" to perform the transplant, which must be signed by a person responsible for the recipient patient previously to transplant, a "Notification of Performed Transplant," and a "Notification of Side Effects." All documents duly completed by the transplant physician must be returned to the tissue bank for traceability control of the procedure and subsequent archiving [2].

Clinical Use of Allogeneic Skin

The main clinical indications for the use of allogeneic skin are deep and extensive burns and large skin defects caused by trauma. One of the most critical factors in handling and repairing lesions in patients with major skin loss is adequate coverage of the damaged area to prevent further blood loss and opportunistic bacterial infections [5].

The gold standard in surgical treatment in these cases is autologous skin grafting. However, this approach is somewhat limited when large extensions of skin are affected or large areas are injured by physical trauma, because of the restriction of skin donor sites in the affected patient. In these cases, utilization of allografts is a providential treatment and can mean the difference between life and death for these patients, with a reduction in mortality from extensive burns when this alternative is provided [5]. Observations of the clinical course of patients with full-thickness burns has shown that the earlier the removal of necrotic tissue and healthy tissue grafting is performed, the better can the recovery outcome [6, 7].

Burns

Skin defects may occur for many reasons, including skin diseases, acute trauma, chronic wounds, or even surgical interventions. However, the most common cause for their occurrence is thermal injury whereby large areas of skin may be damaged, often without the possibility of regeneration [8]. These defects compromise the functional integrity of the skin because they break the electrolyte homeostasis and alter the internal temperature control resulting from an immediate loss of physical barrier. This loss causes body fluids to directly come into contact with the environment and are lost through evaporation that causes severe dehydration in the individual [7, 9].

Classification of Burns and the Use of Allogeneic Skin

First-Degree Burns

First-degree burns affect the topmost layer of skin, the epidermis. The injured area presents hyperemia and painful erythema. Important electrolyte or clinical changes do not occur. Allogeneic skin grafting is not indicated for this type of burn [9, 10].

Second-Degree Burns

A second-degree burn reaches beyond the epidermis into the dermis layer and may be superficial or deep. Its main characteristic is the formation of blisters (bubbles containing liquid formed beneath the epidermis) which can rupture easily, leading to exposure of the dermal layer. Re-epithelialization results from the migration of cells in the basal layer of the annexes (sebaceous and sweat glands, and hair follicles) to the surface, with resolution of the lesion within 15–20 days after trauma [9, 10].

As a result of capillary stasis in the bed of burning during the first 48 h, there is the chance of bed drying, making the burn deeper. This can be prevented by an allogeneic skin graft within

the first 6 h after the occurrence of the burn. A significant reduction in pain is immediately apparent after the application of the graft. At first, the donor skin is sticky and remains in place as a flexible graft. In general, rapid epithelialization follows and the graft begins to dry and detach [9, 10].

Third-Degree Burns

In third-degree lesions there is necrosis of the epidermis and dermis, with destruction of all dermal attachments as well as the nerve endings, with consequent anesthesia of the damaged areas. The healing process in these cases is time consuming and delicate, requiring appropriate management of the patient. After surgical removal of necrotic tissue, the wound can be covered with autograft depending on the availability of healthy donor regions and the clinical condition of the patient. This graft can be covered with an allogeneic skin graft, known as "sandwich" or mesh graft, which provides cover for the exposed areas. In cases where there is no possibility of autografting or when the patient has a more delicate clinical condition, the exclusive use of allogeneic skin is possible. The time to permanence grafted tissue at the injury site ranges from 3 to 5 weeks [9, 10].

Skin Defects Caused by Trauma

The allogeneic skin can also be used to cover skin defects caused by trauma, such as scalping and amputations [9, 10].

Chronic Wounds

The allogeneic skin preserved in glycerol can be useful as a first surgical step prior to conducting autologous grafts in cases of chronic wounds. This tissue has a stimulating effect by cleaning and granulating the wound bed. An important effect is the reduction of pain [9, 10].

Glossary

Allogeneic skin   Skin from an individual of the same species, but genetically distinct.
Autograft transplantation   A skin graft transplantation from a donor area of the same patient.
Cryopreservation   Preservation method of cells and tissues consisting in a progressive and slow decrease of temperature which, when combined with the use of cryoprotectants and buffered saline solutions, maintains cell viability.

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Marketing Influence on Body Image Perception: A Bioethical Perspective

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Key Points

- There has been a steady increase in the search for aesthetic-related procedures in the medical field
- The controversy about plastic surgery is based on the analysis of the patients' reasons for requesting surgical treatment
- Patients who undergo aesthetic surgery are members of a group of particularly vulnerable people
- Mass media plays a huge role in spreading stereotypes related to the aesthetics of body image
- Concerns about body image are often influenced by the media and social networks, leading to unhealthy behaviors

Introduction

Modern society has encountered countless ethical dilemmas in recent decades, mostly attributable to technological progress in biomedical sciences. These dilemmas may be related to the need to establish limits to the use of new technologies in order to ensure the integrity of people and all components of the environment [1].

Revolutionary advancements have occurred in the understanding, development, marketing, and dissemination of medical knowledge. There have recently been significant changes in the methods of research and practicing medicine, as well as in the variety of services that are considered relevant to healthcare. Linked to industrial progress, advances in medical technology have been remarkable. Sophisticated technologies have expanded the limits of diagnosis on one hand, and of intervention efficacy on the other [2].

This new scientific and technological reality, whose impact on the global economy is substantial, began about half a century ago. Undoubtedly, its capacity of transforming and intervening in the environment and in the human species has caused scientific and ethical perplexities for some time. Among the several healthcare technological innovations with immediate repercussions on people's lives, the production of highly potent antibiotics, assisted reproduction, gene therapy, and the use of new materials and medications in the field of aesthetics are worthy of mention. Furthermore, consumerism has led the world to a market economy, contributing to a situation whereby wealthy nations maintain other peoples under their economic, ideological, and, in some cases, religious domination [3].

A recurrent issue in today's society is how to establish limits between normal and abnormal,

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natural and artificial. Are people willing to break the rules of anatomic and physiologic normality they have created? Will they be dissatisfied with merely adapting their biological structure for the preservation of the species [3]?

Health sciences have seen a constant increase in the demand for aesthetic procedures. New techniques and products with this purpose have appeared on the market, and countless aesthetic clinics have opened across the world.

In the field of aesthetic surgery, bioethicists have focused on the discussion regarding freedom and autonomy of individuals requesting a procedure. However, aspects such as social pressure and the fact that the human body has been converted into a depository of contemporary society's imaginary ideals should be considered. This situation leads to the analysis of a patient's vulnerability and medical responsibility, which is much higher in aesthetic surgery than in cases with clear clinical indications or in medical emergencies [4].

Thus, a question arises: What would be the reason for patients to be increasingly seeking procedures aimed at improving or changing their appearance? Evidently, every human being is concerned with personal aesthetics. Everyone wants to have a pleasant appearance and good health. However, is this search for aesthetic procedures always aimed at improving the patient's health? What is the limit between health and sickness in the pursuit of an often unreachable perfection? All such aspects are inserted in a new form of reflection, so-called bioethics, which seeks to establish a dialogue between health sciences and morality. This reflection is an attempt to understand the consequences of the application of human knowledge for life and for the future of our planet [3].

Aesthetics

The word "aesthetics" derives from the Greek *aisthetiké* and means to perceive, to feel. It is a branch of philosophy concerned with the nature of beauty. Yet, how can we define what makes something beautiful? What are the traits and features that make a person beautiful? Are such standards constant over time [5]?

Throughout history, great philosophers have tried to define what makes something beautiful. For Plato (428–347 BC) and René Descartes (1596–1650), beauty would be inherent to the object, not depending, therefore, on the subject that perceives it. For Aristotle (384–22 BC), people are responsible for seeking the ideal of beauty, by means of order, proportion, and symmetry. For Hegel (1770–1831), beauty would be inherent to each individual's spiritual activity. In the Middle Ages, the concept of beauty was directly related to identification with God, and Thomas Aquinas (1225–1274) was the most important representative of that time. Finally, for David Hume (1711–1776), the taste for the beautiful would come from each individual, not being directly linked to the object itself [5].

As we can see, not even great philosophers have been able to determine what makes something beautiful, what is universally pleasing with no clear explanation. Then why do beauty standards change so frequently? How can aesthetic standards present, for instance, in Renoir's works, in which female bathers exhibit curvy, voluptuous bodies, have completely changed into today's anorexic standards? We need, therefore, to reflect on the relentless quest for bodily perfection through medical and dental procedures, which often offer great risks to the patient's health and are sometimes unnecessary or even futile.

Naini, Moss, and Gill have questioned whether human notions of facial beauty depend on each person's sense of perception or whether this sense is common to all persons. Is facial beauty a quality of the face observed, or does the sensitivity of the observer also depend on his or her own ideas, feelings, and judgments? The authors quote the philosopher David Hume (1741), who said "Beauty in things exists in the mind that contemplates them," and the writer Margaret Wolfe Hungerford (1878), famous for the sentence "Beauty is in the eye of the beholder." Both quotations, and their philosophical ideologies, assume that sensitivity is subjective to each person. However, if a specific face is universally pleasing, some part of our sensitivity must be common to all human beings [6].

Aesthetic Surgery and Bioethics

The popularity achieved by aesthetic surgery, the development of technological resources, and the proliferation of aesthetic clinics and cosmetic methods indicate the social pressure that currently exists, as a result of intolerance toward old age and the need to conform to universal and cultural standards of beauty. The strategies to confront this need or social desire have challenged the field of bioethics in an almost unprecedented way. Based on bioethics, we should ask ourselves: "For what purpose or reason should I analyze the case of a patient requesting an aesthetic treatment, if their decision is founded on the ultimate expression of freedom and autonomy of being or looking the way they like, and also if the satisfaction of this desire reflects directly on their project and quality of life?" So far, both plastic surgeons and general surgeons have been governed by the same morality and similar codes of ethics.

The term "aesthetic" is broad, since it includes all body interventions, with no necessity of experiencing psychological suffering. Such interventions are part of a satisfaction, a vanity, and a submission to a society that has placed a commercial aesthetic value on bodily beauty, through which it often profits [4].

The controversy over plastic surgery arises from the questioning of psychologists, anthropologists, sociologists, feminists, physicians, and even the general population about the motivation of those requesting an intervention. Assessing the patient's mental health is essential. Excessive concern is expressed by those undergoing aesthetic surgery when they do not adapt to social and cultural standards of beauty, according to the dictates of fashion. Body dissatisfaction, often imperceptible to others, may cause great psychological suffering, resulting in pain, shame, rejection, and emotional and mental instability, reducing the level of personal satisfaction. Since these are all subjective factors, adopting a common standard to all individuals is impossible. This suffering is rooted in the desire and the imagination of beauty. Thus, physical and mental well-being should guide us for meeting the patient's needs [4].

Patients undergoing aesthetic surgeries are part of a particularly vulnerable group. Therefore, they should receive special attention and care in order to prevent physical and mental issues derived from both interventions and results that do not meet their often unrealistic expectations [4].

In aesthetic surgery practice, there are two types of ethical issues. The primary issues arise when decision-making about a surgical procedure involves few ethical issues, because these individuals evidently suffer from a body malformation, such as congenital malformations and injuries caused by burns or serious accidents. The secondary issues, however, are seen with distrust and some ethical objection, because they are superficial or vanity-driven interventions that may unnecessarily place a healthy body at risk in order to improve its image, such as liposuction, rhinoplasty, facelift, and abdominoplasty [7], which often do not have medical indications or are even contraindicated in some cases.

The World Medical Association (WMA) Declaration on aesthetic treatments adopted at the 65th General Assembly, which took place in October of 2014 in Durban, South Africa, establishes ethical principles to be observed in aesthetic treatments (Box 54.1). According to the WMA, aesthetic treatment is defined as an intervention performed not to treat a lesion, disease, or deformity, but for nontherapeutic reasons, with the sole purpose of improving or changing the patient's physical appearance [8].

Box 54.1 Ethical Principles to Be Observed in Aesthetic Treatments Defined by the World Medical Association [8]

Ethical principles on aesthetic treatment

1. The patient's dignity, integrity, and confidentiality must always be respected

2. Physicians have a role in helping to identify unhealthy body images and to address and treat disorders when these exist

3. Aesthetic treatments must only be performed by practitioners with sufficient knowledge, skills, and experience of the interventions performed

4. All practitioners providing aesthetic treatments must be registered with and/or licensed by the appropriate regulatory authority. Ideally, the practitioner should also be authorized by this authority to provide these specific aesthetic treatments

5. All aesthetic treatments must be preceded by a thorough examination of the patient. The practitioner should consider all circumstances, physical and psychological, that may cause an increased risk of harm for the individual patient and should refuse to perform the treatment if the risk is unacceptable. This is especially true in the case of minors. Practitioners should always choose the most appropriate treatment option, rather than the most lucrative one

6. Minors may need or benefit from plastic medical treatments, but pure aesthetic procedures should not be performed on minors. If, in exceptional cases, aesthetic treatment is performed on a minor, it should only be done with special care and consideration and only if the aim of the treatment is to avoid negative attention rather than gain positive attention. All relevant medical factors, such as whether the minor is still growing or whether the treatment will need to be repeated at a later date, must be considered

7. The patient must consent explicitly to any aesthetic treatment, preferably in writing. Before seeking consent, the practitioner should inform the patient of all relevant aspects of the treatment, including how the procedure is performed, possible risks, and the fact that many of these treatments may be irreversible. The patient should be given sufficient time to consider the information before the treatment starts. When the patient requesting the treatment is a minor, the informed consent of his or her parents or legally authorized representative should be obtained

8. All aesthetic treatments performed should be carefully documented by the practitioner. The documentation should include a detailed description of the treatment performed, information on medications used, if any, and all other relevant aspects of the treatment

9. Aesthetic treatments must only be performed under strictly hygienic and medically safe conditions on premises that are adequately staffed and equipped. This must include equipment for treating life-threatening allergic reactions and other potential complications

10. Advertising and marketing of aesthetic treatments should be responsible and should not foster unrealistic expectations of treatment results. Unrealistic or altered photographs showing patients before and after treatments must not be used in advertising

11. Advertising and marketing of aesthetic treatments should never be targeted to minors

12. Practitioners should never offer or promote financial loans as a means of paying for aesthetic treatment

Next, we discuss some basic concepts of bioethics that are very important to lay the foundations for a reflection about this pursuit of body perfection through medical procedures, which is increasingly influenced by a globalized media and standardized ethical patterns.

Principles of Bioethics

The term bioethics emerged in 1971 with the publication of the book *Bioethics: A Bridge to the Future* by American oncologist Van Rensselaer Potter. The author suggested that there was need for a balanced relationship between human beings and the ecosystem in order to preserve life on Earth [1].

The scope of bioethics has become more comprehensive, especially in terms of biomedical sciences. There is concern about ethics in the care of human beings, whether they are patients seeking health care at public healthcare facilities, private healthcare clinics, and teaching hospitals, or individuals who participate in scientific research.

According to Nunes and Nunes, bioethics consists of a continuous search for wisdom, criticism, and use of information and knowledge to improve living conditions and preserve life. Bioethics involves a combination of humility, responsibility, and rationality aimed both at individual and collective welfare [9].

The purpose of clinical bioethics is to analyze and discuss the application of new values resulting from scientific development within a society

that respects pluralism and accepts the differences. The conflicts that may arise in the patient–healthcare professional relationship must be analyzed according to ethical values; that is, a science of the foundations or principles of actions and moral values that constitute a set of cultural rules that regulate human actions [10].

The book by Beauchamp and Childress, *Principles of Biomedical Ethics*, written in 1979, led bioethics toward a line of thought known as "Principlism," a system of ethics used in the analysis of the problems related to biomedicine based on four basic moral principles to guide decision-making, both in clinical practice and in biomedical research with humans [11].

The four principles are nonmaleficence, beneficence, respect for autonomy, and justice. These are basic principles but are not absolute. Beauchamp and Childress did not establish a lexicographic order between these four fundamental principles. Only the context and the consequences of a specific ethical conflict will be able to establish the criteria to order them [11].

The application of these four basic principles is not an easy task, let alone a conclusive task. However, these principles can help people involved in a conflict seek the most ethical way to act, thus supporting the role of principlism [1].

The Principle of Respect for Autonomy

The word *autonomy* derives from the Greek terms *autos* (self) and *nomos* (rule or law) [11]. The principle of respect for autonomy accepts people's self-determination and their ability to make the best decisions based on what they believe [1]. In the context of clinical bioethics, this basic concept of principlism is the basis of informed consent as an active process in the health professional/patient relationship.

The concept of respect for autonomy is widely used to refer to a decision taken in terms of health care and research, both by patients and research subjects [11]. People must be able to decide on a course of action and implement this plan to practice autonomy [12]. Autonomous individuals act

freely according to their own will. By contrast, people who have reduced autonomy are controlled by others because they are unable to decide or act according to their desires and values. For instance, a person with severe mental disorder is not able to decide on what is best for her/him. Some people may also have reduced freedom, such as prisoners or other institutionalized individuals [11], therefore constituting a vulnerable population.

Hence, two fundamental conditions are necessary for an individual to be able to practice autonomy: freedom (to be free from controlling influences) and ability to act intentionally. However, the principle of autonomy can sometimes be overlapped by another moral principle. Therefore, the individual's autonomy is restricted when, for example, a personal choice is harmful to public health or to another person [11], or even during emergency medical care when the patient is not able to make a decision.

Children and adolescents may not have maturity and ability to make autonomous decisions; nevertheless, this does not mean that they do not deserve moral respect. Their legal guardians are responsible for protecting them and making the decisions. Clinical studies involving children and adolescents require the participants to sign an informed consent form in order to show their willingness to participate in the study. However, an informed consent form must also be signed by the participant's legal guardian, and must be written in a clear manner so that the child or adolescent is able to understand it.

The Principle of Nonmaleficence

The principle of nonmaleficence consists of a moral obligation not to create harm to the patient intentionally [12]. This obligation is often stricter than the obligation to help the patient. In any particular case health care may cause little harm to the patient, such as bleeding caused by needle puncture, but, at the same time, may confer greater associated benefit, such as the cure of a disease. Therefore, the obligation of beneficence takes priority over the obligation of nonmaleficence [11].

The Principle of Beneficence

The principle of beneficence is aimed at assuring the patient's well-being and interests according to the criteria of beneficence provided by the healthcare facility where people are seen. In practice, this principle involves using all skills and technical knowledge available to provide health care to patients to increase benefits and reduce risks [1].

Common morality requires us to contribute to other people's well-being. Based on the ethical principles, moral is responsible for determining what is "good" in a scenario or situation and measuring the weight of "good" against the risks in specific actions [12].

Morally, people must be treated not only with respect for their autonomy and without associated harm, but the treatment must also contribute to their well-being. The principle of beneficence is potentially more demanding than the principle of nonmaleficence, because the actions should be positive in helping others and not merely avoiding harmful acts [11]. Medical procedures that neither cause direct benefit to the patient nor produce harm can be described as futile treatments.

The Principle of Justice

The principle of justice is associated with equity issues related to the distribution of healthcare services, respect for people's rights, and respect for the laws morally accepted by the population [12]. The term "justice" cannot be confused with the term "moral." Justice is a moral principle, whereas the law enforces this principle within social life. According to Beauchamp and Childress, the principle of justice is a distributive expression of justice, that is, a fair, equitable, and appropriate distribution in society, according to rules that establish the terms of social cooperation [11].

The Patient–Health Professional Relationship and Decision-Making

Health interventions are focused on diagnosis and preventive or therapeutic treatment to achieve the maximum benefit for each patient. In addition, in clinical practice, risks are justified by the potential benefits associated with the procedure for each patient [11].

The medical visit is a factor that has an impact on autonomy and vulnerability. During these visits, patients deliberately express their willingness to change their bodies, talking about their reasons, desires, or fantasies, and trusting the physician to make their desires come true. After considering the type of treatment requested by the patient, the surgeon often lists the procedures that could improve the patient's appearance [4].

All procedures and techniques aimed at changing the body at the expense of health, putting the patient at risk, should be deeply analyzed considering their ethical aspects. No clinical or surgical intervention in the human body is totally safe. Biomedical or biotechnological interventions should be carried out according to ethical conducts consistent with the physical and moral integrity of the person [3].

However, there has been considerable discussion about the patient's role in decision-making in clinical situations that often involve conflict between respect for the patient's autonomy and care for his/her health, and between the patient's values and the health professional's values [13].

Unlike the old Hippocratic model, patients' needs, values, and moral principles must be taken into consideration. Patients can actively participate in decision-making in unique situations in their lives [14]. Health professionals keep their authority because they hold the technical knowledge on indications and contraindications of a specific treatment, always taking into account the needs and wishes of the patient. However, health professionals cannot transfer the full responsibility for these choices to patients, thus becoming mere service providers [11].

Hence, in an optimal model of the patient–health professional relationship, the professional is not the only one responsible for making the decisions. Instead, the decision-making process must be based on mutual and respectful participation. The role of health professionals is to help patients understand their situation and their illness, evaluating possible courses of action and

expressing their desires and values. In this relationship, health professionals provide their scientific knowledge, including knowledge on different options available for the diagnosis and treatment of the patient's condition. At the same time, patients express their goals and values, according to which the risks and benefits of various treatment options can be evaluated. Based on this approach, choosing the best treatment for each specific patient includes the participation of both the patient and the health professional [13]. The decision is made with both agents sharing the responsibility. The patient expresses his or her will, and the health professional holds the scientific knowledge and is responsible for determining the most recommended actions for each case.

Informed Consent

As already mentioned, the principle of respect for the patient's autonomy is essential to understanding the informed consent as an active process in the patient–health professional relationship.

The code of ethics of health professionals and the standards for research involving human beings require the signatures of an informed consent form. Informed consents are required to make it possible for persons who undergo medical treatment or participate in studies to make independent choices, thus protecting patients and research subjects from harm. Such consents are also aimed at encouraging health professionals and researchers to take responsible actions when dealing with other people's life and health [11].

The objective of requiring patients and research subjects to provide informed consent is neither to protect health professionals against possible negligence claims nor even to produce evidence of good clinical practice. The main objective is to provide patients with all the information they need to make an autonomous decision in accordance with their interests. Therefore, providing informed consent is an active process of mutual decision-making to reduce the risk of alleged illegal actions. Communication between patients and health professionals is the beginning of a trust-based relationship [15].

Thus, the informed consent form should not be a document solely aimed at providing legal protection for health professionals. Instead, it should be an active process of mutual decision-making between patients and health professionals, considering technical issues (of professional responsibility) as well as the patients' values [16].

It is worth noting that judging values is a complex task because each individual has his or her own peculiarities. Therefore, it is essential that health professionals are aware of all the facts related to specific cases and that patients receive clear information on all possible outcomes of a specific treatment, as well as the risks and consequences that may arise. Only then will patients be able to decide on what they believe to be the best for them in an autonomous and informed manner.

Every patient must be respected, especially regarding the privacy and confidentiality of their data. Also, whenever there is associated conflicts of interest, this should be made clear to patients.

Aesthetic Medicine and the Media

Aesthetic medicine covers all types of medical procedures aimed at improving patients' physical appearance and psychological satisfaction by means of noninvasive or minimally invasive techniques for cosmetic procedures [17]. In a systematic review assessing the effect of experimental presentation of thin media images on body satisfaction, Groesz et al. [18] concluded that, from a sociocultural perspective, mass media disseminates a slender ideal that can lead to body dissatisfaction [18].

In a meta-analysis on the role of the media in the concepts of body image among young women, Grabe et al. [19] found that the body image shown in the media is directly related to women's widespread dissatisfaction with their own bodies, higher expenses to change their body appearance, and increased number of eating disorders. These effects are present in several outcomes in both experimental and correlational studies. Therefore, exposure in the media seems to be negatively related to women's body image regardless of assessment method, differences in

individual variables, media type, age, or other characteristics of the studies. In addition, based on the result of this meta-analysis, the authors emphasized the importance of prevention and intervention, particularly in education and advertising. In terms of education, the media can be used to teach girls and women to become more active and more critical consumers of products related to body appearance to prevent the development of body dissatisfaction and disturbed eating behaviors. The use of models with medium-sized bodies in advertisements could help protect some women from developing body dissatisfaction or at least prevent the exacerbation of strict concepts about body image [19].

The current sociocultural theory provides a robust theoretical basis for understanding body dissatisfaction, claiming that the slender ideal is enhanced by various social influences [20]. The media is the most powerful and widespread type of influence [18].

Women who see skinny models in media images tend to have negative feelings about their bodies; and this is particularly truer for overweight women, because there is a larger discrepancy between the size of their bodies and those typically thin images shown in the media today [21].

Bergstrom, Neighbors, and Malheim conducted a study evaluating the effect of the media on body image disorder in 197 university students. The objective of the study was to investigate whether women who were overweight would care more about their appearance after seeing thin women in media images. The authors found that women with low self-esteem related to their body mass index cared more about their appearance after seeing images of thin women in comparison with women with high self-esteem or those who did not see the images. They also reported that the magnitude of the threat to the perception of their own body image depends, among other factors, on the discrepancy between their bodies and the comparison target [21]. Prieler and Choi stressed that the concern with body image dissatisfaction should go beyond the slender ideal as it may be related to various body parts, such as breast size, skin color, and shape of the eyes [22].

Mass media plays a huge role in spreading stereotypes related to the aesthetics of body image. The media can also establish and reinforce the standards for a perfect male body, emphasizing leanness and muscularity. Taking part in conversations on social networks about physical appearance may increase perceptions that the ideal male body is slim, tall, and muscular. Social media can also have a significant impact on body image in some men when they compare themselves with real or computer-manipulated muscular figures [23].

The interactive format and content of social media, such as the strong presence and exchange of multiple images, suggest that social media can significantly influence body image concepts through negative social comparisons [23]. Social media and contemporary digital technologies represent the arena where lessons are learned, attitudes are adopted, and body image concepts are created, disseminated, and transformed into strong beliefs [23]. Unlike conventional media, the Internet and social networks enable users to create and share messages in a streamlined manner. In addition, instant communication with other users on mobile devices is also made possible [23].

Body Image Disorders

As mentioned earlier, concerns with body image, often influenced by the media and social networks, exceeds a healthy limit when disorders related to body image are developed both in women and men. Diseases such as body dysmorphic disorder (BDD) and dysmorphophobia are increasingly common, affecting both men and women at different ages and from different sociocultural groups.

BDD has been included in the International Statistical Classification of Diseases and Related Health Problems (ICD-10 Version: 2016) of the World Health Organization, in Chapter V of the Mental and Behavioral Disorders within Somatoform disorders (F45), being classified as a hypochondriacal disorder (F45.2) [24]. Its essential feature is a persistent preoccupation

with the possibility of having one or more serious and progressive physical disorders. Patients manifest persistent somatic complaints or a persistent preoccupation with their physical appearance. Normal or commonplace sensations and appearances are often interpreted by patients as abnormal and distressing, and attention is usually focused upon only one or two organs or systems of the body. Marked depression and anxiety are often present, and may justify additional diagnoses. The following conditions are classified as hypochondriacal disorder: body dysmorphic disorder, dysmorphophobia (nondelusional), hypochondriacal neuroses, hypochondriasis, and nosophobia; as well as delusional dysmorphophobia and fixed delusions about bodily functions or shape, which are classified as schizophrenia, schizotypal, and delusional disorders [24].

Dysmorphophobia is a psychiatric condition that is often diagnosed in doctor's offices. This disorder is problematic for patients and can be confusing for health professionals. A commonly undiagnosed condition, it can be detected by a few simple steps. Referral to a psychiatrist can be beneficial for most patients suffering from this disease [25].

When body dysmorphophobia is a possible diagnosis, any medical treatments with aesthetic purposes should be avoided and patients should be referred to a mental health center. This is very important for the patient's mental health but also because it is unlikely that the patient will be satisfied with the results of any aesthetic interventions [26].

Individuals with BDD may develop a variety of compulsive behaviors related to the body part of interest [27]. These behaviors are called compulsive because they occur repeatedly. Some examples include checking a specific part of the body in the mirror, comparing their body with other people's bodies, repeatedly using makeup, or camouflaging a body part with clothes [27].

BDD is a condition associated with dissatisfaction with physical appearance in combination with repetitive behaviors associated with these defects. BDD affects both men and women with approximately the same intensity, but a variant called muscle dysmorphia develops more often in men [28]. Muscle dysmorphia is a pathologic concern that the body is not muscular enough. It occurs as a relatively new form of body image disorder in men. Men with this disorder believe that they are small, when they actually are of normal size or even very muscular. Men with any type of BDD should be carefully evaluated for the presence of muscle dysmorphia, because men with concerns about other parts of their bodies may also have muscle dysmorphia, which appears to be associated with a major psychopathology [29].

Pope et al. [29] evaluated men with BDD and compared those with a history of muscle dysmorphia with those with BDD who did not have muscle dysmorphia. Men with muscle dysmorphia were similar to other men in terms of demographic factors, severity of BDD, delusion, and number of body parts with related muscular dissatisfaction [29].

Future Perspectives

As we can see, marketing has a negative influence on body image perception in both men and women from different sociocultural groups, bringing many severe diseases. Ethical dilemmas, such as respect for autonomy, can arise when an increasing number of patients seek perfection in their bodies through aesthetic procedures.

We must reflect on this incessant search for perfection of the body through medical and dental procedures, which can bring risks to patient health and often be unnecessary or futile.

It is therefore essential that prevention of such body image disorders becomes a major priority in the care of human health. This can be achieved by using the media to spread concepts of health and to prevent the development of body dissatisfaction and disturbed eating behaviors.

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Quality of Life in Dermatology

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Key Points Summary

- This chapter presents the importance of quality of life evaluation in dermatology, and the clinician's role in this new treatment approach
- Reviews and describes quality of life scales used in dermatology in general
- Sets scales used in pediatric dermatology and their importance in treatment compliance
- Provides, in addition, information about specific scales made for particular dermatoses and family members

Introduction

Quality of life (QoL) is an expression that suggests considerable interpretation and involves important issues such as social welfare, health, family, prosperity, emotional condition, and others [1, 2]. This expression was clearly defined by the Quality Group of Life from the World Health Organization (WHO) as "the individuals' perception of their role in life, in the context of culture and value systems in which they are supported to, and in related to their goals, expectations, standard of living and concerns" [3].

Dermatologic diseases frequently have an unpleasant effect on patients' emotional conditions, social life, and daily activities because of the stigmas resulting from the lesions' appearance [4, 5]. It is estimated that one-third of dermatologic patients have emotional aspects associated with their dermatosis [6]. Because of the common trajectory between ectoderm, skin, and the central nervous system, they present a close connection. This connection leads to the assumption that the skin and central nervous system can influence each other, which has been shown in several studies of skin diseases, such as systemic lupus erythematosus, psoriasis, acne, and alopecia areata. In these specific dermatoses it is clear that an unbalanced psychic condition can be triggered and negatively exacerbated by the underlying skin disease [7–9].

Moreover, the context of psychological distress related to acne does not affect only the patient. Considering health as a multifactorial concept, family members are also affected by the consequences of acne, and they too could develop emotional disorders. According to a dermatologic study in 2013, conducted by researchers from southern Brazil, this connection between psychological factors and dermatosis is substantive. The authors pointed out that 42% of

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caregivers of pediatric patients suffering vitiligo had anxiety symptoms and 26% had depressive symptoms [10].

The importance of having standard tools that consider QoL is based on the appreciation of the patient's subjective experience of living with the disease. This subjective aspect is a measure of the relationship between the patient's living conditions and psychosocial state. Monitoring the report from the patient's point of view on the feelings regarding the disease is the best way to conduct an assessment of QoL [11].

The analysis of the responses in QoL questionnaires allows clinics to accurately set this connection [12]. In arbitrary clinical trials, the estimation of QoL was recently added as the third dimension to be studied in addition to the efficiency and safety of the medications [4]. Tools that assess QoL should not be limited to the reporting of symptoms but should also include the way the patient faces the disease and its improvement [13].

Table 58.1 Main scales measuring quality of life in a global evaluation of the patient

Name of scale	First time mentioned in	Version in Portuguese
WHOQOL-100 (World Health Organization Quality of Life Assessment)	The WHOQOL Group [3]	WHOQOL-100 Fleck et al. [14]
WHOQOL-Bref	The WHOQOL Group [15]	WHOQOL – Bref Fleck et al. [16]
SF-36 (36-Item Short Form Health Survey)	Ware et al. [18]	Brasil SF-36 Ciconelli et al. [20]
NHP (Nottingham Health Profile)	Lindholm et al. [21]	Perfil de Saúde de Nottingham Teixeira-Salmela et al. [22]
SIP (Sickness Impact Profile)	Gilson et al. [23]	PSIP Feio et al. [26] (Portuguese version for Portugal)
PGI (Patient-Generated Index)	Ruta et al. [30]	–

State of Art

The assessment of QoL in dermatology as measured by scales began with the Dermatology Quality of Life Index (DLQI) designed by Finlay and his team [1]. Since then, the use of similar instruments has become increasingly common. Moreover, it is confirmed as valid and effective, a fact that indicates QoL as one of the pillars of medical care in dermatology and a standard part of routine clinical dermatology [13].

The use of QoL questionnaires, associated with both detailed study of subdivisions covering the different areas that constitute the concept of QoL to be evaluated, and the use of more than one scale for the same analysis, constitutes an effective tool.

Quality of Life Scales in General

Questionnaires for QoL assessment can be applied in three forms: by personal interview or phone, by mail, or by self-application. The first requires more resources, but ensures compliance and reduces errors and losses; the second is

cheaper, but increases the number of losses because of lower reliability of the data; while the third reduces errors and losses, but is limited by its simple structure. Besides these there is a form of administration by Internet, which is not very practical [2]. The most widely used tools for global patient consideration nowadays are listed in Table 58.1.

World Health Organization Quality of Life Assessment (WHOQOL-100)

Given the importance of the concept of QoL and after several discussions about questionnaires that assess QoL, the WHO developed, in 1994 [16], a tool whose intention is general in nature [3]. The WHOQOL-100 consists of 100 items that assess QoL in six areas: physical, psychological, level of independence, personal relationships, environment, and spiritual aspects/religion and beliefs [18]. This instrument, also valid for Brazilian practice [14], although rather comprehensive and complete, requires a long time for its completion, making it difficult its use in routine care.

WHOQOL-Bref

Because of the time taken for completion of WHOQOL-100, in 1998 the same WHO group developed the WHOQOL-Bref, a shorter tool with similar internal validity. It consists of 26 questions, two of which are related general issues of QoL; the other questions are divided into four areas: physical, psychological, personal relationships, and environment [16].

The 36-Item Short-Form Health Survey (SF-36)

This instrument evaluates both the health condition and the QoL generally, and is used in research and clinical practice [17–19]. It can be implemented by phone or interviewer, or be self-administered. It consists of 36 items, divided into eight areas: functional capacity, physical aspects, pain, general health, mental health, emotional aspects, social functioning, and vitality. It also contains a question of comparative assessment between current mental health conditions and the same conditions 1 year previously [18]. Despite being relatively short, it is a comprehensive questionnaire with broad coverage of all areas related to the concept of health, enabling the detection of small to moderate differences among groups [18, 19]. It can be used by different populations to allow comparison between several diseases [20].

Nottingham Health Profile (NHP)

The NHP was developed in England and was also validated in Switzerland. It considers questions about the patient's discomfort related to pain, physical mobility, sleep, energy, emotional reactions, and social isolation, items presented in the first part of the instrument, and has been used to check the impact on QoL of chronic leg ulcer patients [21, 22].

Sickness Impact Profile (SIP)

This tool is not connected to the disease diagnosis but considers the patient's conduct, and is

considered widely applicable among different diseases and cultural groups [23, 24]. It is a validated, estimated, and effective instrument to assess the health conditions of a specific population and the changing nature of these conditions over time, or also to compare different population groups [23, 25]. It covers appropriate healthcare effects and can be used for assessment, planning, and formulation of health policy, aiming not only at improving mortality/morbidity rates but also reducing the impact of diseases on daily activities [23, 24]. The SIP is composed of 136 statements about health related to disorders in 12 areas of activity, and can be self-administered; it has a Portuguese version fulfilled in Portugal [23–26]. The respondent points out only those statements that seem to be true at that time [23]. There is an English version of the SIP, the UKSIP (United Kingdom Sickness Profile), in a similar format to the previous one, but with particular percentage results. It has high internal consistency and reproducibility and has been used for psoriasis [27], acne [28], and atopic dermatitis (AD) [29].

Patient-Generated Index (PGI)

The PGI is a three-step assessment instrument developed in 1994. As a first step, the patient sets the five most affected areas by disease; in the second step, the patient grades the less important to more important areas that affect life quality between 0 and 100; and finally the patient shares "60 points" among the listed items according to his/her concept of necessity of improvement in those areas. The index ranges from 0 to 100: the higher the score, the lower the QoL. The purpose of this questionnaire is to calculate the effect of the disease on QoL according to relevance in the context of daily life as estimated by the patient [30].

Quality of Life Scales in Dermatology

The development and the confirmation of specific QoL questionnaires for Dermatology is a new tool of assessment [31]. General questionnaires, used for all types of dermatoses, allow comparisons

Table 58.2 Main scales measuring quality of life in a dermatologic evaluation of the patient

Name of scale	First time mentioned in	Version in Portuguese
DLQI (Dermatology Life Quality Index)	Finlay et al. [5]	DLQI Ferraz et al. [48]
Skindex	Chren et al. [38]	Skindex-29 Paula et al. [52]
DSQL (Dermatology-Specific Quality of Life)	Anderson et al. [37]	–

between them and also an overview of their involvement in the patient's QoL. These questionnaires can be applied to patients in different clinical categories and can also be applied to groups under control [19]. There is also a trend toward the combination of two questionnaires, a general and a dermatologic one, with combined evaluation of each measurement [32]. In addition, there are questionnaires for childhood dermatosis, some of them containing images [33–35].

The most validated and currently used questionnaires are the DLQI (Dermatology Life Quality Index) – QoL Index for Dermatology, Skindex (with its simplified version, Skindex-29) m and DSQL (Dermatology-Specific Quality of Life) – Specific QoL for Dermatology. These instruments are self-applicable, reproducible, with shelf life and acceptable confidence [36–38]; some of these tools can even be sent by mail [19, 35, 39], as described below and summarized in Table 58.2.

Dermatology Life Quality Index (DLQI)

In 1995, Finlay et al. [5] created and validated this instrument in order to allow simple, minor, and regular assessment of skin diseases in general, such as psoriasis [40–43], AD [41, 44], other eczemas [40, 43], and vitiligo [45]. The questions refer to facts from a week before the administration of the questionnaire, which can be completed in about 3–5 min, and are relevant to outpatients aged between 15 and 75 years [5, 36].

The instrument consists of ten items divided into six groups: symptoms and feelings, daily activities, recreation, job, school, personal relationships, and treatment. Responses set scores of 0–3, and the final calculation is a simple sum of these scores, with the highest rates indicating the worst QoL associated with the disease [5].

This tool is easily used in many contexts, such as clinical or research situations, for inpatients, outpatients, or control patients [19, 36, 46, 47]. By the end of 2003, the DLQI was translated and validated in Brazil in 2006 [48], allowing the assessment of the impact of diseases such as alopecia areata, Darier's disease, lichen planus, and viral warts [49, 50].

Skindex-29

The Skindex-29 is a simplified version of the self-administered questionnaire Skindex. This version, widely used at present, was designed in 1997 and contains 61 items divided into eight levels: cognitive effects, social effects, depression, fear, embarrassment, anger, physical discomfort, and physical limits [38].

The Skindex-29 version contains 29 items and an additional one related to adverse effects of treatment, divided into three different parts: symptoms, functionality, and emotions [51]. The probable answers are: never, rarely, sometimes, often, and always, given in a scale from 1 to 5 points, with the final score calculated either by the average of obtained points from the 29 questions (total score) or by the average from the items of each domain (domain score). In Brazil the validation and adoption of this tool is recent, being conceived in 2014 [52].

Dermatology-Specific Quality of Life (DSQL)

The DSQL was developed as an easy to use comprehensive tool for use in dermatologic clinical trials and observational studies [37, 53]. It is more elaborate and takes longer in its application (15 min) than previous versions. It contains 52 items, 43 of them specific and nine related to emotional well-being, in general,

taken from the SF-36 questionnaire. It includes seven different levels: physical symptoms, day-to-day activities, social functioning, general mental health, vitality, job functionality, and school [37].

Quality of Life Scales Specific for the Evaluation of Pediatric Patients in Dermatology

At present, the estimation of the QoL in pediatric patients is relevant in medical practice. Because of this, in randomized clinical trials it has been added as a third particular aspect to be studied besides the safety and efficacy of the medication [54].

Dermatoses are taken as a relevant subject, given the aspects of negative psychological impact the disease confers, such as problems in the cognitive process, and difficulties in school learning and in the social and family environment. In addition, the disease could cause mild to severe mood disorders and personality disorder. Moreover, even interest in sports activities can be adversely affected by skin disease because of its strong relationship with low infant self-esteem [55].

In an extensive study of skin disease in the United Kingdom including a group of 64 pediatric patients with pruritus, AD, or psoriasis, a relationship between clinical worsening and an adverse event in patients' life was observed. As a result, a clinical improvement occurred 5 years later, after these stress factors were removed [56].

Over recent years further studies evaluating the QoL in children with specific dermatoses such as AD [57], vitiligo [58] and epidermolysis bullosa [59] have been conducted worldwide, reflecting the increasing importance of this aspect of treatment, demonstrating a shift in the relevant position of improving the effectiveness of health care for such conditions.

A study conducted in São Paulo in 2008 compared pediatric patients with chronic diseases with apparently healthy patients and observed a lower QoL in patients with chronic

diseases using the Quality Index Pediatric Life (PedsQL) questionnaire. The study distributed the questionnaire separately, with the same queries, among pediatric patients and the relative who was accompanying them to consultations, whereby a correlation between the information in the physical and educational aspects was observed, but there was disagreement with their views on the psychological aspects [60]. Another study has successfully applied the PedsQL, translated to Portuguese, in pediatric patients with neoplasms [61].

The family impact that acne causes is extremely important in the treatment and needs to be addressed during patient care, since the child's environment is greatly affected by conditions caused by the disease, in addition to the stigma suffered. The need to evaluate the QoL of the family heralds the development and improvement of this type of analysis in order to effectively evaluate how the disease can change the functioning of the group [57–59].

This section describes the most widely used scales for the assessment of QoL in pediatric patients (Table 58.3).

Table 58.3 Main scales measuring quality of life in a dermatologic evaluation of the pediatric patient

Name of scale	First time mentioned in	Version in Portuguese
PedsQL (Pediatric Quality of Life Inventory)	Varni et al. [62]	BR-PedsQL Scarpelli et al. [61]
DFI (Family Dermatosis Family Impact)	Lawson et al. [94]	O Impacto da Dermatite Atópica Infantil na Família Weber et al. [66]
CDLQI (Children's Dermatology Life Quality Index)	Lewis-Jones et al. [33]	BR-CDLQI Prati et al.[63]
IDQoL (Infants' Dermatitis Quality of Life Index)	Lewis-Jones et al. [35]	Índice de Qualidade de Vida da Dermatite Atópica em Crianças Alvarenga et al. [109]
AUQEI (Quality of Life Scale for Children)	Manificat and Dazord [64]	AUQEI Assumpção et al. [65]

Pediatric Quality of Life Inventory (PedsQL 4.0)

The general questionnaire PedsQL assesses items in physical, emotional, social, and educational dimensions. The PedsQL (Pediatric Quality of Life Inventory™) version 4 [61] has 23 issues in: (1) physical dimension (eight items); (2) emotional dimension (five items); (3) social dimension (five items); and educational dimension (five items). These dimensions were developed by discussion groups, cognitive interviews, pretests, and protocols of mensuration development. Completion of the tool takes 5 min [62]. It is compose by parallel forms of self-evaluation of children's and parents' questionnaires. The child self-evaluation includes children aged 5–7, 8–12, and 13–18 years. The parents' questionnaire includes ages 2–4 (preschool), 5–7 (toddler), 8–12 (child), and 13–18 years (teenager), and assesses the parental perception of QoL in the child. Besides the PedsQL, other questionnaires have been developed to evaluate relatives' QoL.

Children's Dermatology Life Quality Index (CDLQI)

This questionnaire was made to assess the QoL of patients aged 4–16 years, presenting a structure similar to that of the DLQI and FDI [33], and a scale that assesses pediatric patients' welfare in dermatologic-specific fashion, with the goal of allowing a simple, compact, and uniform assessment in several contexts for patients presenting general dermatologic disease such as psoriasis, AD, other eczemas, vitiligo, and nevus.

The CDLQI tool in its nonillustrated form was previously translated and validated in Brazil by Prati et al. as *Escore da Qualidade de Vida na Dermatologia Infantil*. Besides giving a general index of QoL related to the patient's skin disease, it helps to assess how each patient's life aspect is affected [63].

This tool consists of ten questions subdivided into six categories: symptoms and feelings, daily activities, recreation, school, personal relation-

ships, and treatment. The answers score between 0 and 3 and the final count is a simple sum of these scores. The highest score indicates the worst QoL related to the evaluated disease.

In 2003, a more appealing illustrated version of the CDLQI emerged [34]. Colorful and friendly dog drawings were added to questions, keeping the original text. The comparison among the versions shows that they produce similar results, suggesting that they may be equivalents. However, the illustration was quickly adopted as it was considered easier by children and parents.

The Infants' Dermatitis Quality of Life Index (IDQoL)

The IDQOL was developed as a method to assess impairment of QoL in infants with AD in a clinical setting and in conjunction with an instrument for assessing clinical severity, such as the SCORAD [14] or SASSAD [15].

The IDQOL was derived from parental views of the impairment of QoL caused by their children's eczema. It was produced and validated in 2001, with the goal of assessing children under 4 years old. It is quick and simple to complete, containing ten questions about symptoms and difficulties of mood, sleep (two questions), play time, family activities, mealtime, treatments, dressing, and bathing. The highest score for each question is 3, leading to a maximum total possible score of 30. There is an additional question scored separately, asking for the parents' assessment of current dermatitis severity, giving four options, from none to extremely severe (0–4).

It is sensitive to treatment changes but presents a weak correlation with severity of the clinical condition [35]. It is estimated that some of the parameters used by parents may show some impairment in "normal" infants. The authors demonstrated that the IDQOL is simple to use in an outpatient setting or by postal survey. It is not based on clinicians' views and has been characterized from the test–retest results to have good reproducibility.

The Quality of Life Scale for Children (AUQEI)

The AUQEI was developed by Manificat and Dazord [64], and assessed and translated by Assumpção et al. [65]. This questionnaire gives a profile of the child's satisfaction and welfare degree in different situations, based on four images that represent the answers: very happy, happy, discontented, and very discontented, associated with several QoL domains.

In studies conducted in 2012 in a dermatology referral center in southern Brazil [66], it was observed that the results taken from AUQEI and CDLQI indicate that the general QoL of the child is less affected than the QoL domains specifically related to dermatosis.

Quality of Life Scales in Specific Dermatoses

The QoL assessment in dermatologic patients is affected by the stigma and the disease's presentation characteristics, and for this reason some scales are applied in a specific way, according to the patient's dermatosis, as shown in Table 58.4.

Psoriasis

Psoriasis can initiate deep effects in patients' functionality and welfare [32, 67]. The dermatologic treatments are sometimes only temporary, with a large impact on QoL of these patients. There are several tools for the assessment of QoL in psoriasis, with the correct choice of instrument depending on the study subject, the patient's characteristics, and the psychometric measures of the chosen questionnaire [32, 42]. Among the available tools, the following are worthy of mention.

Psoriasis Disability Index (PDI)

Inability caused by psoriasis is defined by the PDI as practical aspects of a patient's life changed by the disease appearance that can be confirmed by an observer.

Table 58.4   Main scales measuring quality of life in specific dermatoses

Name of scale	First time mentioned in	Name in Portuguese
Psoriasis		
PDI (Psoriasis Disability Index)	Finlay et al. [68]	–
PLSI (Psoriasis Life Stress Inventory)	Gupta et al. [70]	–
PSORIQoL (Psoriasis Index of Quality of Life)	McKenna et al. [71]	–
Acne		
ADI (Acne Disability Index – Índice de Incapacidade para a Acne	Motley and Finlay [76]	–
CADI (Cardiff Acne Disability Index)	Motley and Finlay [77]	–
APSEA (Assessment of the Psychological and Social Effects of Acne)	Oakley [74]	–
Acne-QoL	Martin et al. [79]	–
UKSIP (United Kingdom Sickness Profile)	Salek et al. [28]	–
Vitiligo		
VLQI (Vitiligo Life Quality Index)	Senol et al. [110]	–
VitiQol (Vitiligo Specific Health Related Quality of Life Instrument)	Lilly et al. [111]	VitiQoL-PB Boza et al. [108]
VIS-22 (Vitiligo Impact Scale-22)	Gupta et al. [112]	-
Melasma		
MelasQoL (Melasma Quality of Life Scale)	Lieu et al. [85]	MelasQol-PORT Cestari et al. [86]
Dermatitis of the scalp		
Scalpdex	Chen et al. [97]	–
Atopic dermatitis		
QoLIAD (Quality of Life Index for Atopic Dermatitis)	Whalley et al. [100]	–
ADDI (Atopic Dermatitis Disability)	Eun et al. [101]	–
Itch		
ItchyQo	Poindexter et al. [95]	–
Latex allergy		
QoLLA-C e QoLLA-P (Quality of Life in Latex Allergy – Children and Parents)	Lewis-Jones et al. [107]	–

This scale, translated to Brazilian Portuguese as *Índice de Incapacidade Causada Pela Psoríase*, includes 44 variables distributed as: 28 questions related to loss on daily activities, professional activities, personal relationship, recreation, and treatment, all of them during the last 4 weeks; and nine additional questions that refers to the patient's symptoms and feelings related to the disease. In addition, the involved area is analyzed [68].

Finlay et al., comparing the use of the PDI questionnaire in a compact version (15 questions) with the questionnaire to assess the general SIP QoL, showed a good correlation between these two methods, demonstrating a good applicability of PDI because of the short time necessary for completion [25]. A second study suggests the use of 10 questions from the compact questionnaire (15 questions) proposed by Finlay. The author advocates that three of these questions would not distinguish patients with psoriasis from those with dermatologic conditions, while the other two must be punctuated negatively (the opposite of the proposed, whereby a low assessment would result in a high score) [69].

Psoriasis Life Stress Inventory (PLSI)

The PLSI assesses the resulting stress from the impact of the disease on QoL, involving 15 situations associated with psoriasis and the degree of stress associated with these events. With an average completion time of between 10 and 15 min, it must be used in subgroups of patients with a high psychological impact level associated with the disease [70].

Psoriasis Index of Quality of Life (PSORIQoL)

This is the newest tool to evaluate QoL in psoriasis. McKenna et al. [71] developed 25 dichotomous items, which inform about, among others, issues such as socialization, self-esteem, limitations in personal freedom, emotional stability, and sleep disturbance. The authors claim that the questions do not access direct injuries or deficits, as in the other questionnaires, but highlight the impact of these and other influences in the QoL. The applicability of PSORIQoL in clinical studies has yet to be demonstrated [71].

Acne

Acne causes emotional, social, and psychological changes severe enough to justify specific tools to assess the QoL of these patients [72]. Tools made for acne have been more specific than the general questionnaire [73]. The most widely uses nowadays include the following.

Acne Disability Index (ADI)

Consisting of 48 questions, the ADI has eight dimensions: psychological, physical, recreational, professional, self-image, social reaction, skin care, and financial care [74, 75]. It associates the patient's social and psychological prejudice with the severity of the acne on different parts of the body [76].

Cardiff Acne Disability Index (CADI)

The CADI consists of a form with five questions derived from the ADI [77] and presents good internal consistency in comparison with ADI and UKSIP [17, 31]. It correlates the acne severity on the face and midsection, and is useful to identify patients with low self-esteem who are seeking less invasive treatment, and to assess the treatment effect [77, 78]. Scores, however, do not correlate well with the severity of the clinical condition [74].

Assessment of the Psychological and Social Effects of Acne (APSEA)

This scale was developed by the use of a psychological and social approach in different questionnaires about disability related to acne beyond ADI [79].

Overall, 15 items comprise the APSEA, nine of which are scored on a linear visual analog scale from 0 to 10, and the remaining six by response selection with score allocation of 0, 3, 6, and 9. The maximum achievable score of 144 represents the greatest disability. Although none of the questions are specific for facial acne, the APSEA correlates with facial acne grade but not the total acne grade [80].

Acne Quality of Life Scale (Acne-QoL)

This tool estimates the effect of facial acne in QoL and the impact of treatment in clinical trials.

The 19 questions explore four dimensions: personal perceptions, social life, emotional condition, and symptoms related to acne [81]. The Acne-QoL presents good applicability, shelf life, and internal consistency [82], and the scales of QoL strongly correlate with the severity reported by patients in comparison with that reported by the clinician, suggesting that the patient's perceptions of the disease may be more important than the obtained results [32].

United Kingdom Sickness Profile (UKSIP)

This is the UK version of the SIP, developed by Salek in 1986. It is a self-administered questionnaire containing 136 health-related statements covering 12 areas of daily activity, seven of them aggregated into physical and psychosocial dimensions. The final score is expressed as a percentage. The questions in the UKSIP relate to the situations on the day of completion based on the respondent's usual activity. In addition to the detailed statement questions, patients are also asked to rate their "overall health" on a 5-point scale ranging from "very good" to "very poor" [28].

Vitiligo

Parsad et al., in 2003, evaluated the impact of social and psychological difficulties in treatment response of patients suffering vitiligo, using the DLQI for the assessment. According to the results, a worse index of QoL would be related to responses less favorable to treatments, suggesting that a psychological approach could be more valuable, attesting the importance of measurement not only of lesion severity but also the leverage on patients' day-to-day activity [47]. The QoL assessment of patients suffering vitiligo by the DLQI in a nonclinical scenario also appeared to be effective, but with a weak correlation with sex and age [83].

Vitiligo Life Quality Index (VLQI)

In 2012, Asl Şenol et al., in Turkey, created the VLQI in English, evaluating specifically the QoL in patients suffering vitiligo. The scale is com-

posed of 25 questions that assess emotions, personal relationships, anxiety, work/school life, leisure, and symptoms. The answer for each question can be evaluated as: "never" = 1; "sometimes" = 2; "often" = 3; "all the time" = 4. The total score varies between 25 and 100. Higher scores mean worse QoL.

Vitiligo-Specific Health-Related Quality of Life Instrument (VitiQoL)

In the United States the Vitiligo Specific Health Related Quality of Life Instrument (VitiQoL) has been validated by Lilly et al. It is a questionnaire to specifically evaluate the QoL in individuals suffering vitiligo. The VitiQoL has 15 items, scoring from 0 ("not at all") to 6 ("all the time") for each question, and therefore achieves a total score between 0 and 90. It assesses the domains of participation limitation, stigma, and behavior. Moreover, it presents a personal assessment of vitiligo severity via a scale ranging from 0 (without skin involvement) to 6 (most severe), which leads to the 16th question in the questionnaire. This questionnaire is promising as a study tool, both epidemiological and clinical, presenting very good discriminatory power [17]. In 2014, Boza et al. translated and validated this questionnaire for use in Brazil (the VitiQoL-PB) [108].

Vitiligo Impact Scale-22 (VIS-22)

More recently, in 2014, Gupta et al. validated the VIS-22 questionnaire, which can be used as a guide for therapeutic decisions including psychological interventions in patients suffering vitiligo. It has 22 questions, covering domains of self-confidence, anxiety, depression, marriage, family worries, social interactions, school/college-related, occupation-related, treatment-related, and attitude. Each question is scored as "not at all" = 0; "a little" = 1; "a lot" = 2; "very much" = 3.

Melasma

The Melasma Quality of Life Scale (MelasQoL) is a questionnaire developed and assessed by Balkrishnan in 2003. This new instrument was made for an English-speaking population and

focuses on the effect of melasma on emotional aspects such as attractiveness, productivity, and vitality. It is composed of ten questions, scored from 1 to 7, whereby higher indices indicate a worse QoL.

MelasQoL has a high internal consistency, validity, and a good discriminatory power, meaning that the questionnaire can also be used for other dermatosis. The original MelasQoL study evaluated 102 female patients, aged between 18 and 65 years, most of them being high school graduates (87%) and free of any other disease (64%). The results established that the personal areas most affected by melasma were social life, recreation, leisure, and welfare.

The Melasma Area and Severity Index (MASI) is a tool to evaluate the extent and severity of melasma, however, MelasQoL values bear only a slight correlation with this scale demonstrating that, for patients, the impact of the disease is typified by criteria other than its clinical severity as assessed by clinicians. This difference clearly illustrates the need to broaden the evaluation of therapeutic results and possibly how dermatologic consultations are conducted. MelasQoL has been translated and adapted culturally for Spanish and Brazilian Portuguese-speaking populations in accordance with WHO guidance and other published recommendations [6, 17].

Recently, Balkrishnan et al. developed the MELASQOL (Melasma Quality of Life Scale), which collects valuable information about the impact of this dyschromia. It has high internal consistency, shelf life, and good discriminatory power in comparison with other questionnaires [84–86].

Contact Dermatitis

The recurrent characteristic of this disease confers an important social and occupational impairment, mainly if there is hand involvement. There is no specific questionnaire for QoL measurement in contact dermatitis, so clinicians usually resort to a general questionnaire in combination with a more specific one [19, 51, 87].

Dermatitis of the Scalp

The Scalpdex was developed in 2002 for the assessment of QoL in patients with psoriasis and seborrheic dermatitis on the scalp, and consists of 23 questions divided into three tables [88]. When compared with Skindex, this questionnaire showed better capacity of response detention over time [89].

Atopic Dermatitis

AD is a characteristically recurrent disease whose symptoms usually appear during childhood, and in which one-third of patients retain the disease in adult life [35]. Psychological aspects and emotional stress have a role in its pathogenesis [90, 91]. The difference between clinical severity and the socio-psychological impact of the disease illustrates a need to expand the assessment of therapeutic results and the integral attendance of patients.

Quality of Life Index for Atopic Dermatitis (QoLIAD)

This is the most specific tool to analyze QoL in patients with AD. It was developed and initially validated in 1994, with the intention being applied to literate adult patients without other conditions that could influence the QoL. It is composed of 25 items, each with a simple and dichotomous response system, making its use simple and rapid. It is available in English, German, French, Spanish, Italian, and Dutch languages. Among the tools compared in the initial study, it presented the closest correlation with the DLQI [92].

Atopic Dermatitis Disability Index (ADDI)

The ADDI was developed in 1989, with 11 questions referring what happened in the previous 12 months [93]. Because of its evaluation format it is considered a long-term perception of the patient's QoL and has not been used frequently in practice, since the evolution of QoL during treatment is not easily accessed by this method.

Pruritus

Pruritus is a common symptom that is present in several dermatoses. Recently the measurement of its impact on QoL has been made possible by a specific tool, the ItchyQoL, which contains 27 questions and was validated in English [95]. Initial studies demonstrated it to be a questionnaire with sufficient sensibility to detect the emotional, functional, and symptomatic impact between different levels of severity and frequency of pruritus [96, 97].

Quality of Life Assessment in Family Members

It is known that diseases have a significant impact not only on patients' lives but also that of their relatives and partners. Thus, questionnaires to assess QoL in relatives are of major importance. It is well known that when the relatives' QoL is affected they find it more difficult to give support to the sick patient. The following describes the noteworthy questionnaires that assess this aspect (Table 58.5).

Pediatric Quality of Life Inventory: Family Impact Module (The PedsQL Family Impact Module)

The PedsQL™ measures parent self-reported physical, emotional, social, and cognitive functioning, communication, and worry [98]. It presents 36 items and was designed to measure the impact of pediatric chronic health conditions on relatives, similar to the DFI scale, which measures parent-reported family daily activities and family relationships. The Brazilian version was validated by Scarpelli et al. in 2008 [99].

Family Dermatology Life Quality Index (FDLQI)

The FDLQI is a questionnaire designed for adult relatives or partners of patients with any skin

Table 58.5 Scales measuring quality of life in family members

Name of scale	First time mentioned in	Version in Portuguese
The PedsQL family impact module	Varni et al. [62]	The Brazilian version of the PedsQL™ family impact module
		Scarpelli et al. [61]
DFI (Family Dermatosis Family Impact)	Lawson et al. [67]	Weber et al. [113]
FDLQI (Family Dermatology Life Quality Index)	Basra et al. [100]	–
PIQoL-AD (Parents' Index of Quality of Life in Atopic Dermatitis)	McKenna et al. [103]	–
CADIS (Childhood Atopic Dermatitis Impact Scale)	Chamlin et al. [104]	–
PFI-15 (Psoriasis Family Index)	Eghlileb et al. [105]	Boza et al. [106]

disease. As it is self-explanatory, the FDLQI is an easily administered questionnaire. Its scoring is calculated by summing the score of each question, resulting in a maximum of 30 and a minimum of 0 [100]. As in the DLQI, the higher the score, the more the QoL is impaired. There is as yet no validated version of this instrument for the Brazilian setting.

Dermatitis Family Impact (DFI)

In the adapted Brazilian version, the DFI examines the consequences of AD involvement in pediatric patients in daily life [66, 101, 113]. Consisting of ten questions, it analyzes the impact of dermatosis in the child's and relatives, lives in the week before the appointment, including several daily domains common to a family, such as sleep, recreation, feeding, and house cleaning. Considering that the disease affects an individual's QoL and its role in triggering and worsening of some dermatoses, the search for more data about this relationship is needed to help improve therapeutic evaluations and behavior in the pediatric patient population [94, 102].

Parents' Index of Quality of Life in Atopic Dermatitis (PIQoL-AD)

The PIQoL-AD instrument was developed for the UK, Netherlands, Italy, France, Germany, USA and Spain. It has 28 dichotomous items, making it short and practical to use, and is designed to be completed by the parents of children aged 8 or younger. It is a valuable instrument for inclusion in clinical trials and routine clinical practice. The PIQoL-AD provides distinct and complementary information to existing dermatology-specific measures and has been shown to be responsive to changes in QoL in clinical trials.

The PIQoL-AD assesses the QoL of parents of young children who have AD. It is not intended to measure the direct impact of the condition on the children, although it is likely that this will be related to the impact on the main caregiver. The PIQoL-AD will serve as an invaluable addition to the outcome measures already available for use in dermatology, most notably those assessing functional limitations: the IDQOL for children under 4 years old and the CDLQI for older children [103].

Childhood Atopic Dermatitis Impact Scale (CADIS)

The CADIS is self-administered by the patient's parents. Standardized answers consist of five category choices relating to frequency ("never," "rarely," "sometimes," "often," and "all the time"). The CADIS looks at the parent's perceptions during the last 4 weeks and evaluates the conceptual framework to consist of two dimensions with five domains: child dimensions (symptoms and activity limitation/behavior) and parent dimensions (family/social function, sleep, and emotions). It is a measurement of the effects of AD on young children and their parents [104].

The Psoriasis Family Index (PFI-15)

Several psoriasis-specific QoL instruments are available to measure the impact of psoriasis on patients. However, the impact caused by many skin diseases is not limited to the patient but may extend to the rest of the family.

To this end, Eghlileb and coworkers [105] developed and validated a new tool to assess family members and partners of patients suffering psoriasis, the PFI-15. The questionnaire consists of questions applied to relatives, which evaluate psychological aspects of the disease, collateral effects of treatment, sleep, daily activities such as reading, travel, shopping, and others, with answers chosen from one of four alternatives ranging from "not applicable" to "a lot." It is a questionnaire validated for Portuguese and easy to apply, direct, and complete. The preliminary results are promising [106].

Conclusion

From the clinical point of view, the importance of measurement of QoL is obvious when patients arrive at the clinic with a serious complaint about the effect on daily life that symptoms cause and their perception of welfare, while the assessment of relatives is also essential [103, 107]. Some individuals are more affected than others by the disease, even when the disease severity and length are similar [94]. Several factors affect the degree of impact the disease could have on QoL: the individual characteristics of patients, the disease's natural history, the affected body location, and disease time before diagnosis [51]. To date, QoL questionnaires have been used frequently in clinical studies, showing good correlation with other analyzed characteristics [107]. The assessment of QoL in general patient evaluation is fundamental in deciding the therapeutic strategy and its course. The development of tools in dermatology that assess this aspect must be increasingly stimulated, not only in respect of translation and validation but also the elaboration of new instruments for different cultures or social groups, following the inevitable evolution of integral care of individuals.

It is clearly important that these instruments are adapted to both the language and culture of each population; as the use of

QoL measures become more commonplace the need for validated, adapted instruments becomes more apparent.

The health of individuals depends on the harmony between the physical, psychological, and social dimensions and correlates directly with QoL, being understood as a multifactorial entity. Thus, the individual's appreciation as a whole and an interdisciplinary intervention are imperative for any therapy to be effective in improving patients' QoL.

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Dermatoscopy in the Public Health Environment

56

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Key Points

- Dermoscopy has been shown to improve diagnostic accuracy, sensitivity, and specificity of skin cancer diagnosis
- If you don't have a dermoscope … You can always perform tape dermoscopy!
  - Use immersion fluid (i.e., water, olive oil, disinfectant spray) to place it on the flat or slightly elevated lesion;
  - Cover the lesion with transparent adhesive tape with lateral tension;
  - Use ambient indoor or outdoor lighting for illumination (rather than flash photography);
  - Position your photographic device at an angle of approximately 45° from the side of the lesion to avoid light reflection;
  - Record a focused image with your mobile phone or digital camera at a distance of approximately 25–30 cm from the lesion; and
  - Enlarge the image on the screen of the device.

  Done! Even though you have better have your own dermoscope!

- Interpretation of colors and structures is essential for dermoscopic diagnosis since both have a histopathologic correlate. Recognition of specific structures permits the classification of a lesion as a melanocytic or nonmelanocytic tumor
- Through dermoscopy four main morphologic groups of benign nevi can be identified: globular, reticular, starburst, and structureless blue nevi. There are some special nevi due to their specific body site (facial, acral, nails, mucosal).
- The atypical nevus is not a precursor of melanoma but a risk marker. Atypical nevus has a higher chance of being a melanoma but not a higher chance of becoming a melanoma. Most melanomas start de novo and not in a pre-existing nevus of any type, and if they start in a pre-existing nevus it is often a completely "benign" nevus and not a large dysplastic one

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- Once the patient is examined clinically and by dermoscopy:
  - Patient who has a single lesion or few lesions: if a lesion seems benign it may be left; but if it is suspicious, it should be removed or monitored, depending on the degree suspicion of malignancy
  - Patient with multiple nevi: start monitoring program with an analytic dermoscopic approach for early diagnosis of melanoma
  - Low-risk patient with a single or a few slightly atypical melanocytic lesions: long term monitoring versus excision

Introduction

Much effort has been made in developing noninvasive in vivo imaging techniques to improve dermatologic diagnostics. Dermoscopy, also known as dermatoscopy, epiluminescence microscopy, incident light microscopy, and skin surface microscopy, is performed using a handheld instrument called a dermatoscope or dermoscope, which has a transilluminating light source and standard magnifying optics (usually 10×). A dermatoscope can diminish the refraction and reflection of light at the skin and facilitates the recognition of colors and structures of subsurface skin located within the epidermis, dermoepidermal junction, and papillary dermis, which are otherwise not visible to the naked eye [1, 2].

Dermatoscopes illuminate the skin by use of light-emitting diode bulbs, with or without the use of polarizing filters. Dermatoscopes using nonpolarized light require direct contact between the skin and the scope, and require a liquid interface, such as ultrasound gel or alcohol, to be placed between the skin and the glass plate of the dermatoscope to overpass refraction and reflection. Thus dermoscopy can be contact nonpolarized, contact polarized, or noncontact polarized,

each of which provides complementary information. A cross-polarized dermatoscope allows visualization of deeper skin structures (60–100 µm), and accordingly may have higher sensitivity for detecting skin cancer based on its ability to enhance the visualization of vascular and crystalline structures, both of which are commonly seen in skin cancer. On the other hand, nonpolarized dermoscopy improves specificity as it permits easier visualization of other superficial structures commonly seen in benign lesions, such as milia-like cysts in seborrheic keratosis [2–4].

This diagnostic technique represents a link between the macroscopy (clinical dermatology) and microscopy (dermatopathology). Besides its relevance for evaluating pigmented structures, dermoscopy enables the recognition of vascular structures and other subtle features that usually are less visible to the naked eye [5]. Dermoscopy has mainly been developed to diagnose skin tumors, especially pigmented tumors, and reduce the number of benign lesion excisions. It has also recently played a relevant role in other diseases including inflammatory and infectious disorders.

Dermoscopy has been shown to improve diagnostic accuracy, sensitivity, and specificity for skin cancer diagnosis by dermatologists [2, 6]. Its accuracy is enhanced if physicians are trained in its use. A nontrained individual has a worse result using dermoscopy than with visual examination [7]. A short training course in dermoscopy increases the diagnostic performance of both inexperienced and experienced dermatologists [6]. The main use of dermoscopy is to aid in the decision of whether to perform a biopsy [2]. It is also helpful in the evaluation of amelanotic lesions and inflammatory and infectious diseases. Furthermore, it helps in the evaluation of treatment for different dermatoses.

Two strategies for the approach to dermatoscopic diagnosis of pigmented skin tumors have been described: the verbal-based *analytic* and the more visual-global *heuristic* method [8]. The analytic method implies the application of a catalog of semantic criteria and thereby the detailed analysis of individual features of a given lesion to reach a logical deductive diagnostic conclusion. The heuristic method evaluates the overall pattern of a given lesion

and relies on a so-called gut feeling or some form of intuition. The diagnostic conclusion is drawn from unconscious insight into given relationships without rational or causal deduction. While being taught an explicit analytic method, a student may develop intuitive heuristic mechanisms independently, so in this chapter we focus on the former approach while the other strategy develops. Both strategies are essential in the diagnostic process as applied by a clinician. On one hand, a clinician needs to learn analytically the "alphabet" of a morphologic medical discipline and, on the other, he or she also needs experience to correctly interpret the many variations that a morphologic structure can show in real life. Tschandl et al. [8], in 2015, described a tendency toward sex-related differences in the improvement of diagnoses depending on the approach used, proposing that women would probably be more likely to learn using the heuristic method.

Lower-Cost "Instruments"

As many medical doctors do not have access to a dermoscope, a simple and cost-effective technique that can be easily used is "tape dermoscopy." One of its disadvantages is that dermoscopic features that are only visible under polarized light, such as crystalline structures, cannot be detected [9]. The technique involves:

1. Placing immersion fluid (i.e., water, olive oil, disinfectant spray) on the flat or slightly elevated lesion
2. Covering the lesion with transparent adhesive tape with lateral tension
3. Using ambient indoor or outdoor lighting for illumination (rather than flash photography)
4. Positioning a photographic device at an angle of approximately 45° from the side of the lesion to avoid light reflection
5. Recording a focused image with a mobile phone or digital camera at a distance of approximately 25–30 cm from the lesion
6. Enlarging the image on the screen of the device

This technique has many other disadvantages and so should be used only in "emergency" cases [9].

Colors and Structures

The principal dermoscopic features for making a diagnosis are the interpretation of colors and structure distribution. Colors and structures have a specific histologic correlation [3, 4, 10].

The number of colors is relevant mainly in melanocytic lesions; most benign ones are monochrome. Polychromy is associated with more advanced malignant tumors [11]. Colors depend on the location of keratin, blood, collagen, and melanin. Accordingly, colors visualized include yellow, red, and white for keratin, blood, and collagen, respectively [2].

Colors for keratin show a yellowish-brown pigmentation, depending on its oxidation process, and the presence of melanin. It is yellow to whitish in cystic lesions, and darker in keratin plugs. Colors for hemoglobin are red, blue, purple, or black depending on its location and on its oxidation and presence or absence of thrombosis. The easiest way to visualize blood vessels is to use a noncontact polarized dermatoscope. If a contact dermatoscope is used, it is beneficial to use ultrasound gel as the liquid interface because it minimizes the pressure applied to the vessels. The analysis of morphology and organization of vessels is a very helpful tool, especially in the recognition of amelanotic lesions as exist in some melanomas. A review of vascular structures is beyond the scope of this chapter [12, 13]. Colors for melanin, because of the Tyndall effect, depend on the depth in the corneous stratum, the epidermis, dermoepidermic union, or papillary dermis; this pigment will range from black to dark brown, light brown, gray, and blue [11] (Fig. 56.1).

At times, the presence of colors seems to incorrectly trump the presence of structures and patterns when making a diagnosis. In 2016 Bajaj et al. proposed that color and color variegation can distract dermoscopy users from recognizing or placing appropriate emphasis on morphologic structures and patterns present in skin lesions, leading to the possibility of misdiagnosis and incorrect prognosis. They concluded that there is no statistically significant difference in the ability of novices to correctly diagnose common cutaneous neoplasms in grayscale versus color

Dark brown: stratum
corneum
Brown: epidermis -Light
brown: superior
dermis

Gray: papillary dermis

Blue: reticular dermis
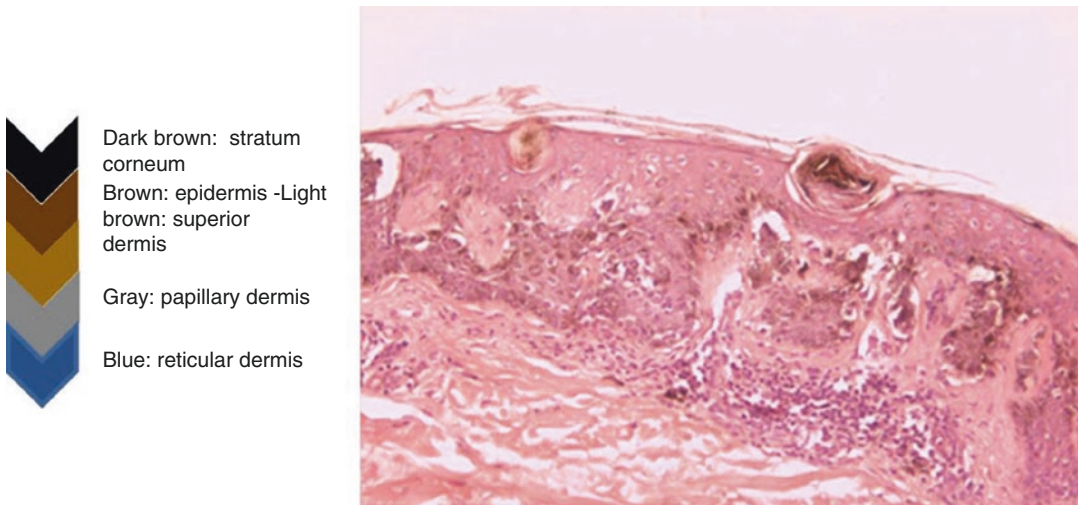
Fig. 56.1 Colors in dermoscopy according to the location of the melanin in the skin

dermoscopic images. Participants were thus able to render a diagnosis based on morphologic characteristics alone (i.e., structure and pattern) without any appreciable loss in their diagnostic confidence level when evaluating grayscale images. These results conclude that dermoscopic diagnosis based on structures and patterns may prove to be more objective and accurate compared with diagnosis based on color [14]. In fact structures have a histopathologic correlate, which is the reason why they help diagnosis. Their recognition is basic for differentiating between melanocytic and nonmelanocytic lesions. The presence of specific structures permits the classification of a lesion as a melanocytic or a nonmelanocytic tumor. An analytic method to classify them is the two-step dermoscopy algorithm [2].

Two Step Dermoscopy Algorithm

The two-step dermoscopy algorithm (Fig. 56.2) guides the observer toward the most likely diagnosis and helps in the decision-making process. This algorithm was introduced in 2001 by a panel of the virtual Consensus Net Meeting on Dermoscopy [15]. Its primary aim is to help clinicians to avoid missing the diagnosis of melanoma, and its secondary aim is to segregate

lesions into melanocytic and nonmelanocytic categories and provide the observer with the most probable diagnosis [2].

The two-step dermoscopy algorithm has high sensitivity, specificity, and accuracy, and can be relied on to provide an accurate and specific pre-biopsy diagnosis and to help guide management decisions. In 2015 Chen et al. reported that there are some lesions that have a higher chance of being misclassified, intradermal nevi being the most common. The authors proposed that other imaging methods such as confocal microscopy may aid in the further evaluation of these lesions. In addition, they arrived at the conclusion that this algorithm helps in maximizing the detection of skin cancer to ensure that malignant lesions are not missed, and aims at making more precise clinical diagnoses [16].

A major critique of the two-step algorithm is that initial errors in the classification of melanocytic status will render the second step irrelevant [16].

First Step: Melanocytic versus Nonmelanocytic Lesions

The first step is to define whether a lesion is melanocytic or nonmelanocytic. The former

Fig. 56.2 Two-step dermoscopy algorithm
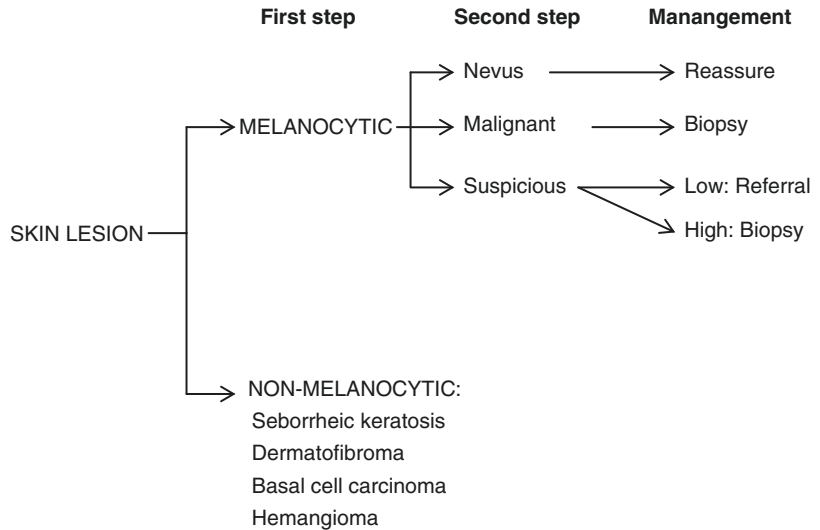
Table 56.1 Melanocytic lesion criteria

Pigment network
Negative pigment network
Aggregated globules
Streaks (pseudopods and radial streaming)
Homogeneous blue pigmentation
Pseudonetwork (facial skin)
Parallel pigment pattern (acral lesions of palms and soles)

should have one of the following criteria (Table 56.1): pigment network, negative pigment network, aggregated globules, streaks (pseudopods and radial streaming), homogeneous blue pigmentation, pseudonetwork (facial skin), and parallel pigment pattern (acral lesions on palms and soles). Lesions classified as non-melanocytic are further subclassified as benign (i.e., dermatofibroma, seborrheic keratosis (SK), hemangioma, and angiokeratoma) and malignant (basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)) in the first step [16]. Lesions that are classified as melanocytic are further evaluated in the second step, which is intended to differentiate benign melanocytic neoplasms from melanoma [2].

If it cannot be defined that a lesion is melanocytic or not it should be classified as suspicious to ensure that cutaneous malignancies will not be missed [17].

Second Step: Benign Versus Malignant Melanocytic Lesions

The second step is to distinguish benign nevi, i.e., melanocytic nevi, blue nevi, Spitz nevi, and atypical nevi, from melanoma [2].

There are multiple methods that can be used to differentiate nevi from melanoma, including pattern analysis, the three-point checklist, the seven-point checklist, the ABCD rule, the Menzies method, the chaos and clues, and CASH (color, architecture, symmetry, and homogeneity) [18]. The first one is preferred by experts, while the others were developed to facilitate a novice's ability to distinguish skin cancer (especially melanomas and BCC) from nevi with high diagnostic accuracy [2, 16, 18].

Here we explain two methods: the three-point checklist and pattern analysis. The three-point checklist is considered the simplest method for novices to learn and use while pattern analysis is the more holistic and complete, and is the most chosen by experts.

The three-point checklist has the highest sensitivity for identifying melanoma [2]. It is intended as a screening algorithm for detecting skin cancer (melanoma and pigmented BCC) and applies only to pigmented skin lesions. One point is assigned to each of the following criteria present in the lesion [19]:

- Asymmetry in distribution of dermoscopic colors and/or structures in one or two perpendicular axes. The contour or silhouette of the lesion does not factor into whether the lesion is symmetric or not.
- Irregular or atypical pigment network consisting of thick lines and irregular holes.
- Blue-white veil and/or white scar-like depigmentation and/or blue pepper-like granules.

A total score of 2 or 3 is considered positive, in which case the lesion should be biopsied or the patient referred for further evaluation [19]. Given its simplicity and high sensitivity for detecting pigmented skin cancer, the three-point checklist may be ideally suited for clinicians with little experience in dermoscopy and for use as a screening tool in the primary care setting [2].

Pattern analysis is a qualitative method that evaluates dermoscopic structures and their distribution [20].

State of the Art

Benign Melanocytic Nevi

Dermoscopy requires the ability to recognize, and experience in recognizing, benign patterns. It also requires the ability to recognize the ten melanoma-specific structures defined by Marghoob et al. in 2013. Any melanocytic lesion that deviates from one of these benign patterns, while also revealing at least one of the ten melanoma-specific structures, should be biopsied to rule out melanoma [2] (Table 56.2).

Through dermoscopy, four main morphologic groups can be identified: globular, reticular, starburst, and structureless blue nevi. There are some structural combinations of the precedent morphologic groups: diffuse reticular, peripheral reticular with central hypopigmentation, patchy reticular, peripheral reticular with central hyperpigmentation, peripheral globules/starburst, peripheral reticular with central globules, and two components symmetric in structure [2] (Figs. 56.3, 56.4, 56.5, 56.6, and 56.7).

Table 56.2 Ten suspicious structures for melanoma adapted from Marghoob et al. [2]

Irregular or atypical pigment network
Negative pigment network
Streaks
Off-centered blotch
Atypical dots or globules
Regression structures
Blue-white veil overlying raised areas
Atypical vascular structures
Crystalline structures
Peripheral brown structureless areas and shape of the holes
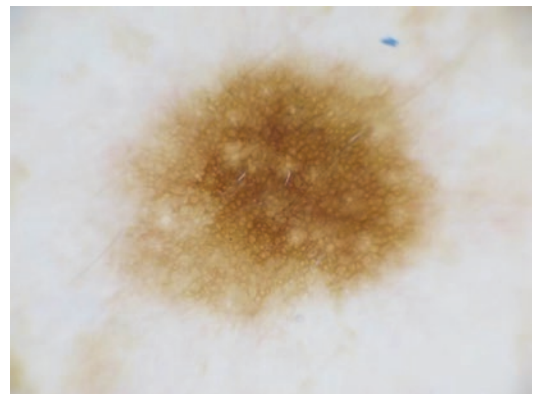
Fig. 56.3 Diffuse reticular pattern in a melanocytic nevus
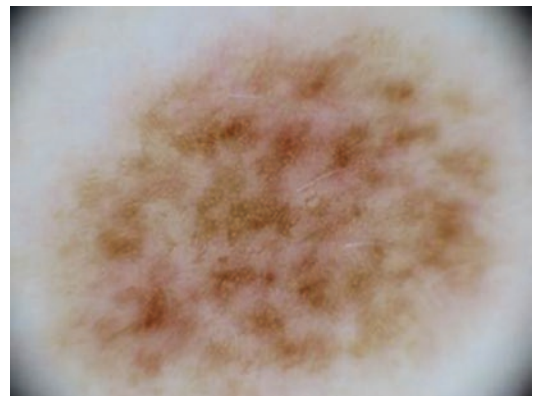
Fig. 56.4 Patchy reticular pattern in a melanocytic nevus

Some nevi are specific according to their special body site: face, acral (palms and soles), and nails. Another group, called special nevi, consists of nevi typified by peculiar clinical–histopathologic findings. These can be subdivided into "melanoma
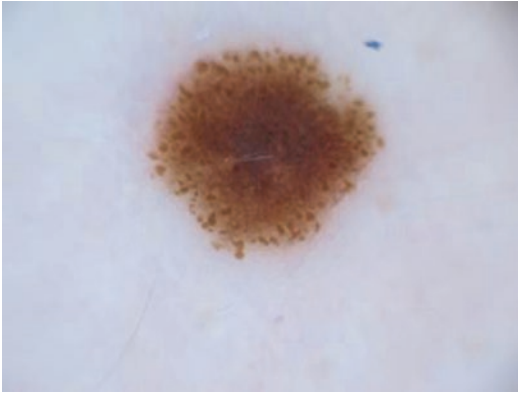
Fig. 56.5 Peripheral globules in a melanocytic nevus
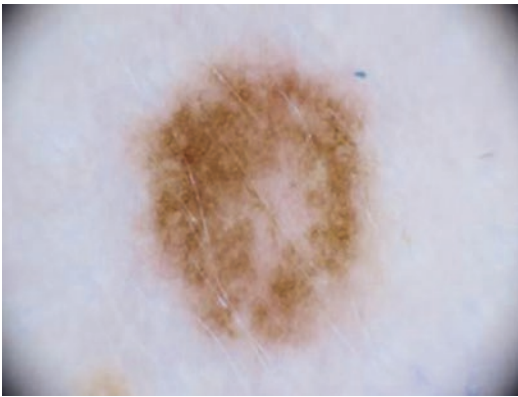
Fig. 56.6 Peripheral reticular with central hypopigmentation in a melanocytic nevus
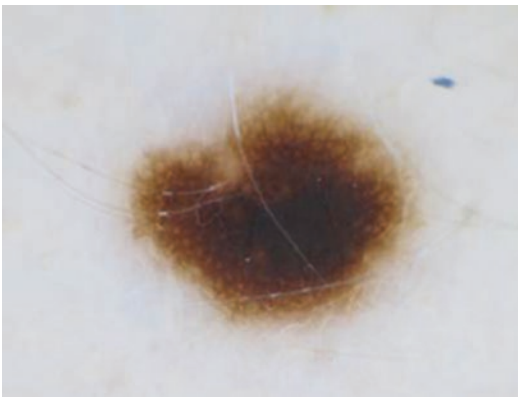
Fig. 56.7 Peripheral reticular with central hyperpigmentation in a melanocytic nevus

simulators" including combined nevi, recurrent nevi, and sclerosing nevi with pseudomelanomatous features, "targetoid" nevi (i.e., halo, cockade,

irritated targetoid hemosiderotic, and eczematous nevi) and uncommon histopathologic variants such as desmoplastic, white dysplastic, or balloon cell nevus. The description of special nevi is beyond the scope of this chapter [21].

Atypical Nevi or Clark Nevus

The term "dysplastic nevus" (DN) is derived from Greek *dys-* (bad or malfunction) and *-plasia* (growth development or change). The name implies that this nevus exists as a different defined entity of potential detriment to its host. Indeed, we prefer to keep this term for histology and preserve the word atypical for clinical and dermatoscopic use. From our point of view, the atypical nevus is not a precursor of melanoma but a risk marker. Atypical nevus has a higher chance of being a melanoma but not a higher chance of becoming a melanoma. Most melanomas start de novo and not in a pre-existing nevus of any type, and if they start in a pre-existing nevus it is often a completely "benign" nevus and not a large dysplastic one [22].

Atypical nevi share some clinical and dermatoscopic features with melanoma so it is often difficult to distinguish one from the other. Atypical nevi are diagnosed with at least three of the following characteristics: (1) diameter more than 5 mm; (2) ill-defined borders; (3) irregular margin. (4) varying shades in the lesion; (5) simultaneous presence of papular and macular components. Dermoscopically they can have three main dermoscopic patterns: reticular, globular, and homogeneous. They have also two descriptors of pigmentation: uniformly and central hypo- or hyperpigmented, eccentric peripheral hypo- or hyperpigmented, and multifocal hypo- or hyperpigmented. Most patients have one type of atypical nevus [23] (Figs. 56.8, 56.9, 56.10, 56.11, and 56.12).

The recently described criteria with strong discriminatory power and moderate levels of interobserver agreement to dermoscopically distinguish nevi from melanoma. Regarding melanoma: architectural disorder, pattern asymmetry, contour asymmetry; and regarding nevi: comma vessels, and absence of vessels [18].
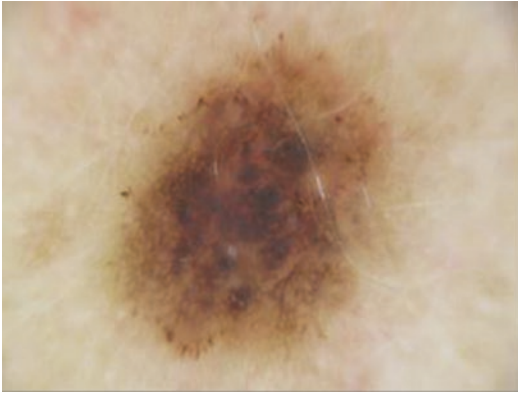
Fig. 56.8 Atypical nevus showing asymmetrical network, irregular margin, irregular size, and distribution of globules

Fig. 56.9 Atypical nevus showing asymmetry and eccentric peripheral hyperpigmented network

Fig. 56.10 Atypical nevus showing asymmetry and peripheral projections and irregular borders

Atypical Mole Syndrome

Some patients have many atypical moles (>5), and there are two options for managing these

Fig. 56.11 Atypical nevus showing ill-defined borders, eccentric hyperpigmented area, irregularly distributed globules, and variegated shades

Fig. 56.12 Atypical nevus showing three main dermatoscopic patterns – globular, reticular, and homogeneous – irregularly distributed in the lesion

patients: removing all atypical lesions, with a high number of unnecessary excisions of benign melanocytic nevi, or dermoscopic follow-up and excision of only those lesions that change over time, considering that probably they were the initial melanomas [24].

Total Nevi, Atypical Nevi, and Melanoma Thickness

A case study from Geller et al. in 2016 of 566 patients in the United States having recently been diagnosed with melanoma demonstrated that most patients had 0–20 total nevi and absence of atypical nevi, this finding being most pronounced among older patients, for whom both total nevi and atypical nevi were uncommon. Therefore, physicians and patients should not rely on the total nevus count as a sole reason to perform skin examinations or to determine a

risk status patient. Younger should be educated on their incresed risk of thicker melanomas, which is associated with having more atypical nevi [25].

Nevi in Specific Body Sites

The anatomic structure of specific body sites results in unique dermoscopic features.

Facial Nevi

On the face, differential diagnoses of pigmented skin lesions are lentigo maligna (LM), LM melanoma, seborrheic keratosis, actinic lentigo, pigmented actinic keratosis (AK), and lichen planus-like keratosis.

Stratum corneum of facial skin is thinner than that of the trunk and limbs, while pilosebaceous units and sweat glands are densely present in the facial skin. The thin epidermis allows blood vessels or melanophages to be observed more easily on facial skin than elsewhere on the extrafacial skin. In addition, the pseudonetwork and sun-damaged elastosis are often present (Fig. 56.13). Facial nevi are usually characterized by unpigmented or poorly pigmented elevated lesions, which correspond histopathologically to dermal nevi [26].

Acral Volar

Saida et al. first performed dermoscopic studies of nevi and melanomas located on the palms and soles in 2002 [27].
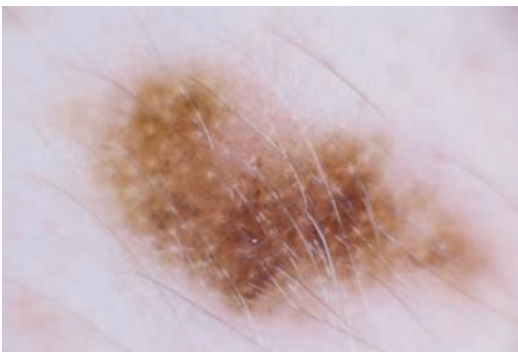
Fig. 56.13 Facial nevi showing a pseudonetwork
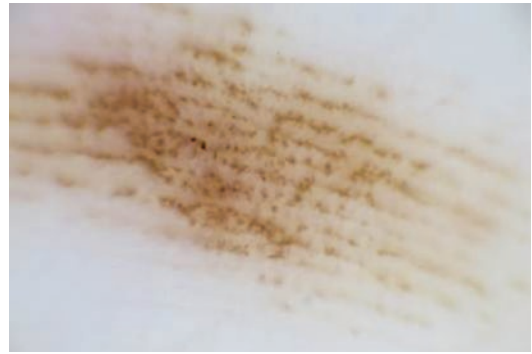
Fig. 56.14 Acral melanocytic nevus showing a parallel furrow pattern
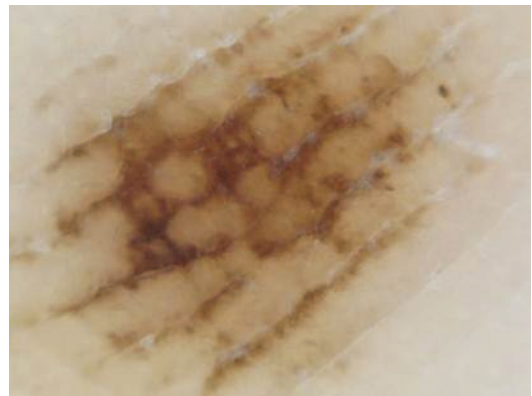
Fig. 56.15 Acral melanocytic nevus showing a lattice-like pattern

Specific dermoscopic major benign patterns are [28–30]:

1. The parallel furrow pattern with its variants, whereby pigmentation is seen in the parallel sulci of the skin (Fig. 56.14)
2. The lattice-like pattern, characterized by pigmented lines that follow and cross the skin margins (Fig. 56.15)
3. The fibrillar pattern, consisting of pigmented lines that cross the skin markings diagonally (Fig. 56.16)

Other patterns are: the nontypical (showing neither malignant features nor the benign patterns described above), the globular pattern (brown globules regularly distributed within the lesion, Fig. 56.17), the homogeneous pat-

Fig. 56.16 Acral melanocytic nevus showing a fibrillar pattern
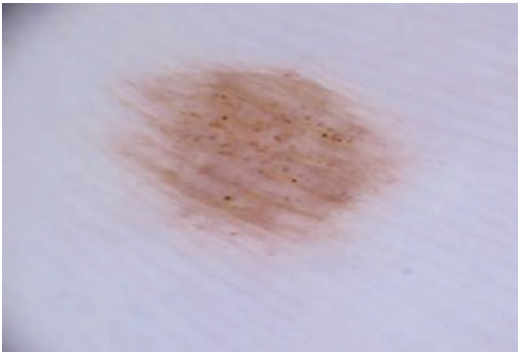
Fig. 56.17 Globular acral pattern

Fig. 56.18 Reticular acral pattern

tern (diffuse light brown or blue pigmentation), the reticular pattern (black or brown network similar to that seen in nonglabrous skin, Fig. 56.18), the transition pattern (combination of specific dermoscopic features characteristic of volar and nonglabrous skin, Fig. 56.19) and
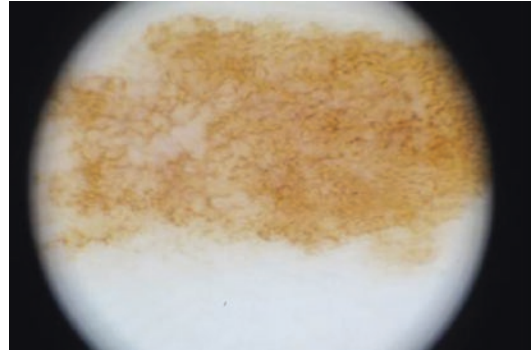
Fig. 56.19 Acral melanocytic nevus showing a transition pattern

globulostreak-like pattern (dark brown globules and brown linear or curvilinear streak-like structures) [28, 29, 31, 32].

All of these patterns are similar among populations worldwide. In our study, performed in the Latin American population, the parallel furrow pattern, followed by the lattice-like and homogeneous patterns, were the most prevalent acral melanocytic nevi [33].

The fibrillar pattern is exclusively found on the soles of feet, since high-pressure points and shearing forces contribute to its dermoscopic features [32, 34].

Mucosal

Pigmented lesions on the mucocutaneous junction and mucous membrane include mucosal melanotic macule (mucosal melanosis), melanocytic nevus, malignant melanoma, and nonmelanocytic lesions, such as bowenoid papulosis. Nevi of the mucosal membrane tend to be associated with younger age compared with melanoma or melanosis. Clinically they present as single 5-mm to 9-mm flat, slightly elevated, or nodular brown to gray lesions. Common melanocytic nevi on the mucosal membranes are brown to gray symmetric lesions with a globular or homogeneous pattern [35].

Benign vulvar lesions including nevi and melanosis have the following patterns: globular, cobblestone, ring-like, reticular-like, homogeneous, parallel, or mixed [36] (Figs. 56.20 and 56.21).

Fig. 56.20 Globular mucosal pattern
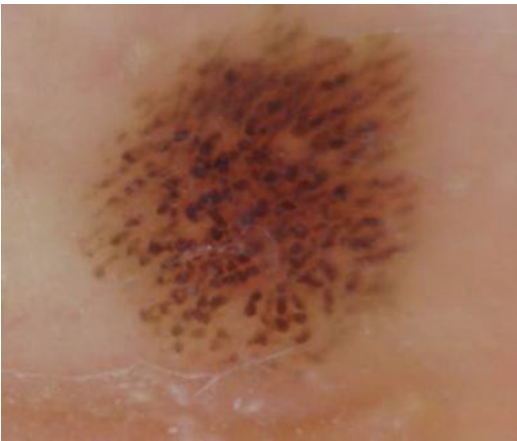
Fig. 56.21 Vulvar globular nevus

Melanoma

Unlike other life-threatening internal cancers, cutaneous melanoma allows diagnosis through noninvasive approaches [37]. The ABCD acronym for melanoma screening was described in 1985 by Riger et al. to provide the lay public and primary healthcare professionals with a useful and memorable mnemonic to aid in the early recognition of potentially curable cutaneous malignant melanoma. It consists of Asymmetry, Border irregularity, Color variegation, and Diameter greater than 6 mm. The E was latterly included for emphasizing change over time as an important additional criterion in differentiating melanoma from benign pigmented lesions [38, 39]. It should be noted that many melanomas do not have all four ABCD features [37]. Besides the

ABCD that helps to recognize an individual lesion, the examination of the rest of the patient's melanocytic lesions is relevant. Another clinical and or dermoscopically important concept is the "ugly duckling" sign, which is a pigmented lesion that "looks different from all of its neighbors," thus arousing suspicion of melanoma [40].

Early diagnosis of melanoma is crucial because its prognosis is directly proportionate to the depth of the neoplasm. The earlier the tumor is detected the thinner it is, so early diagnosis is of central importance in saving lives [37]. In this sense, clinical ABCD seems not enough, as melanoma is already melanoma when it is smaller than 6 mm, and shape, border, and color might be relatively regular at this stage. The advantage of dermoscopy is that equivocal features are often present in very small melanomas, thus increasing our index of suspicion even in the context of small and clinically banal-looking melanomas [24]. The diagnosis of skin cancer, however, is complex, and individual clinicians place varying degrees of emphasis on patient history, clinical evaluation, dermoscopic examination, and heuristic method [8, 41].

Traditional melanoma classification is based on clinical and pathologic characteristics and includes four melanoma subtypes: superficial spreading melanoma, LM, nodular melanoma, and acral lentiginous melanoma [42]. However, today there are other melanomas related to particular genetic status, anatomic location, and degree of sun exposure [43]. Besides the classical melanoma subtypes, here we review the main dermoscopic features of *specific* melanomas: lentiginous nonfacial melanomas in chronically damaged skin, hypomelanotic melanoma, and mucous melanoma. Relevant meta-analysis demonstrated that the use of dermoscopy, for trained users but not novices, improves diagnostic accuracy for melanoma [44, 45].

Regarding the ABCDE rule in melanoma, it should be pointed out that symmetry or asymmetry in dermoscopy does not factor in the contour or shape, but rather the distribution of colors and structures within the lesion, so a lesion could be symmetric for the clinical ABCDE and asymmetric for the dermatoscopic one. Therefore there are
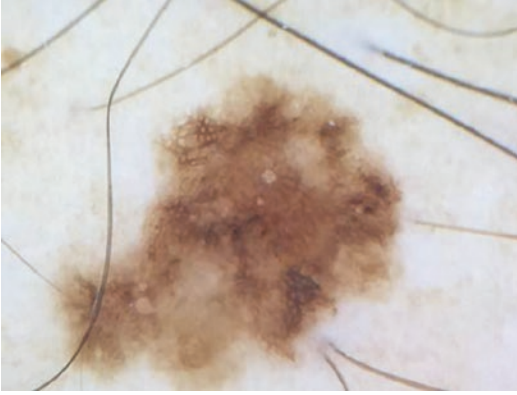
Fig. 56.22 Atypical pigment network, increased variability in the thickness and color of the lines of the network, melanoma in situ

Fig. 56.24 Streaks asymmetrically distributed, melanoma in situ

Fig. 56.23 Negative pigment network. The *circle* marks an area with interconnecting hypopigmented lines resembling a "white network"
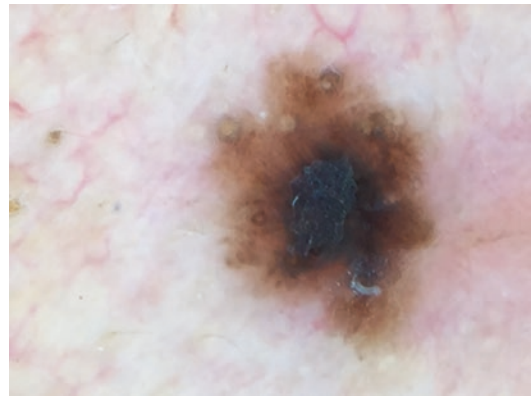
Fig. 56.25 Off-centered blotch

ten melanoma-specific dermoscopic structures as mentioned earlier (Table 56.2) [2]:

1. Irregular or atypical pigment network: Network with increased variability in the thickness and color of the lines of the network, and increased variability in the size (Fig. 56.22)
2. Negative pigment network: Serpiginous interconnecting hypopigmented lines that surround irregularly shaped pigmented structures resembling elongated curvilinear globules [46] (Fig. 56.23)

3. Streaks (pseudopods and radial streaming): Radial projections at the periphery of the lesion that are focally and asymmetrically distributed (Fig. 56.24)
4. Off-centered blotch: Asymmetrically or focally located at the periphery of the lesion. Irregular blotch will often reveal differing hues (Fig. 56.25)
5. Atypical dots or globules: Multiple dots or globules of different size, shape, and color. Asymmetrically or focally distributed within the lesion (Fig. 56.26)
6. Regression structures: Include scar-like depigmentation and peppering, which, when combined, give the appearance of a blue-white veil (Fig. 56.27)
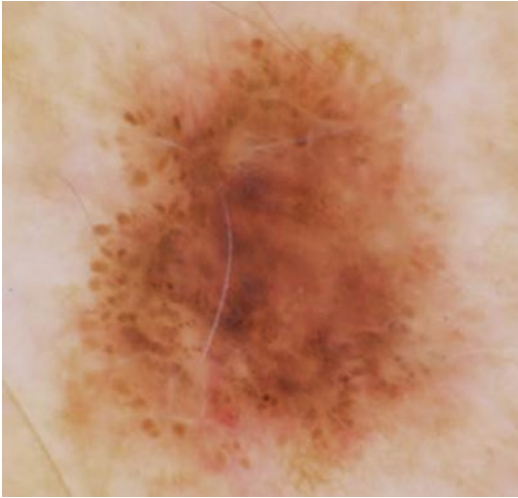
Fig. 56.26 Atypical globules, melanoma in situ

Fig. 56.27 Scar-like depigmentation (*black arrows*) and peppering (*red arrows*) as regression structures. *Yellow arrow*: blue-white veil

Fig. 56.28 Atypical vascular structures, melanoma
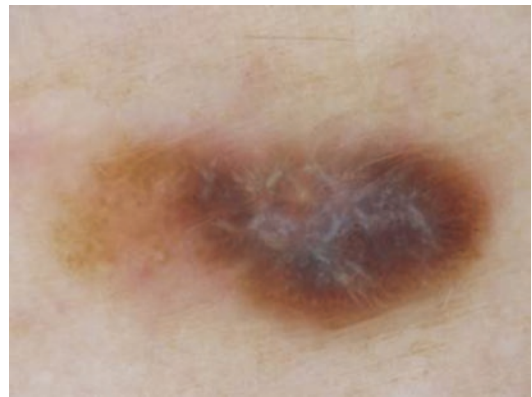
Fig. 56.29 White shiny structures, crystalline structures

white shiny areas: larger structureless shiny areas (Fig. 56.29) [47]

10. Peripheral brown structureless areas and shape of the holes: Tan areas located at the periphery of the lesion that encompass greater than 10% of the lesion (Fig. 56.30)

Nodular Melanoma

Nodular melanoma apparently does not have the initial radial growth phase, beginning with a vertical phase. Nodular melanoma often exhibits features associated with deep tumor extension and less commonly displays the classic dermoscopic features of superficial spreading melanoma [48].

The ABCD warning signs for melanoma were made to identify superficial spreading

7. Blue-white veil overlying raised areas: Tends to be asymmetrically located or diffuse throughout the lesion with differing hues (Fig. 56.27)

8. Atypical vascular structures: Dotted vessels over milky-red backgrounds. Serpentine irregular linear vessels. Polymorphous vessels (Fig. 56.28)

9. White shiny structures, including three groups: (a) crystalline structures: white shiny streaks or lines organized orthogonally or parallel; (b) rosettes: four shiny points; (c)

Fig. 56.30 Peripheral brown structureless areas

Figs. 56.31 Nodular melanoma following the EGF rule (elevated, firm on palpation, continuous growth over 1 month)

Figs. 56.32 Nodular melanoma following the EGF rule (elevated, firm on palpation, continuous growth over 1 month)

Peripheral light-brown structureless areas are absent in nodular melanoma as they are associated with thin melanoma [48]. The main clues for the diagnosis of pigmented nodular melanoma and its differentiation from other pigmented nodular lesions (nonmelanocytic and benign melanocytic nevi) are asymmetric pigmentation, blue-black pigmented areas, homogeneous disorganized pattern, the combination of polymorphous vessels and milky-red globules/areas, and polymorphic vessels associated with homogeneous red areas [48].

The thicker the lesion, the more vascular polymorphism is seen. Blue-black pigmented areas may be the only clue for the correct diagnosis of pigmented nodular melanoma in examining asymmetrically pigmented lesions with a homogeneous disorganized pattern [48, 50].

Acral Melanoma

Four patterns are suggestive of melanoma in acral volar skin: the parallel ridge pattern, irregular diffuse pigmentation, the serrated pattern, and the multicomponent pattern (Fig. 56.33).

Melanoma in Facial Chronically Damaged Skin: Lentigo Maligna

LM has many differential diagnoses in facial skin: actinic lentigo, seborrheic keratosis, pigmented AK, and lichen planus-like keratosis. These are all

melanoma rather than nodular melanoma, as the latter is often small in diameter, symmetric, with regular borders and less color variegation, and is frequently amelanotic [48]. For this reason, the "EFG" rule (Elevated, Firm on palpation, continuous Growth over 1 month) summarizes the classical characteristics of nodular melanoma [49] (Figs. 56.31 and 56.32). The presence of ulceration, a homogeneous disorganized pattern, and homogeneous blue pigmented, structureless areas are significant independent prognostic factors for nodular versus superficial spreading melanoma. Nodular melanoma is frequently symmetric, with regular borders and less color variegation, and is frequently amelanotic. In nodular melanoma the colors are distributed in a disorganized and asymmetric fashion, characterizing the overall disorganized homogeneous pattern [48].

Fig. 56.33 Different images in an acral melanoma of the sole. *Red arrow*: parallel ridge pattern of incipient stages. On the right, multicomponent pattern: parallel ridge pat-tern, fibrillar pattern, irregular diffuse pigmentation, and black eccentric blotch

common facial lesions that typically develop after the fourth decade of life [51]. The lesions have a similar clinical appearance of a flat, pigmented macule of different size and color. Typically solitary lesions appear to be more suggestive of LM, but this difference is not very trustworthy. Accordingly, neither age nor clinical criteria appear useful for differentiating these entities [51].

Throughout this section we describe the dermatoscopic features that differentiate the aforementioned lesions.

Schiffner et al., Stolz et al., and Pralong et al. have identified specific, dermoscopic criteria for facial LM [52–54].

The paradigmatic progression model consists of four subsequent steps of malignancy. The first step consists in regular/irregular, hyperpigmented follicular openings corresponding to the earliest invasion of the hair shaft histopathologically. Subsequently, the signet-ring-shaped structures (thickening of the hyperpigmented follicular openings) and annular–granular pattern (multiple, gray dots and globules round the pilosebaceous units) appear with further invasion. The third step is composed of pigmented, rhomboidal structures that are created in the perifollicular area while progressing. Finally, the follicular opening is completely covered with uniformly
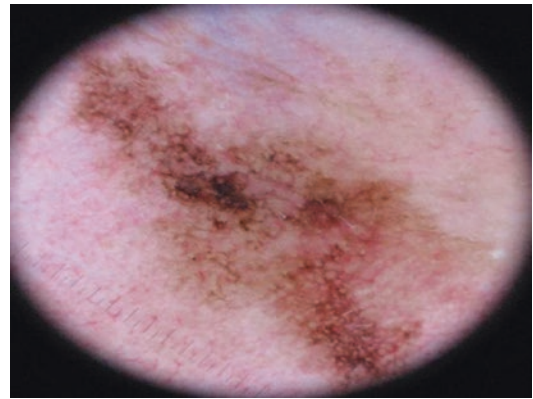
Fig. 56.34 Lentigo malignant melanoma of the face. Hyperpigmented follicular openings. In the center of the lesion, follicular openings completely covered with uniformly pigmented area

pigmented areas. Structureless blue areas, white scar-like areas, and milky-red areas can be also seen [51, 53, 54] (Figs. 56.34 and 56.35).

As characterized by Paralong et al. in 2012, the newly identified dermoscopic patterns include increased density of the vascular network, red rhomboidal structures, target-like patterns, and darkening at dermoscopic examination (when compared with naked-eye examination) [54]. It is very important to never perform ablative treatment of equivocal lesions [51].
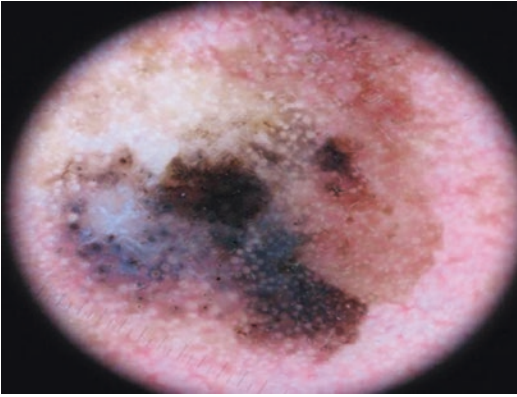
Fig. 56.35 Lentigo malignant melanoma: structureless blue areas and white scar-like areas
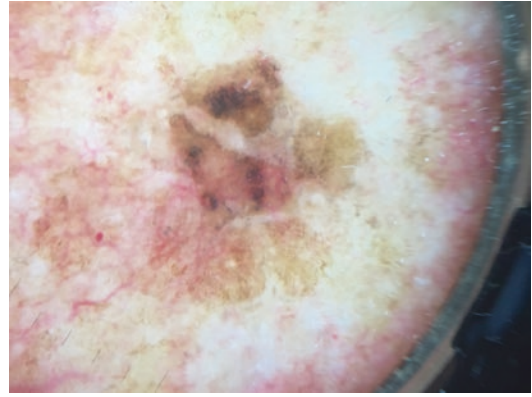
Fig. 56.37 Extrafacial lentigo malingnant melanoma
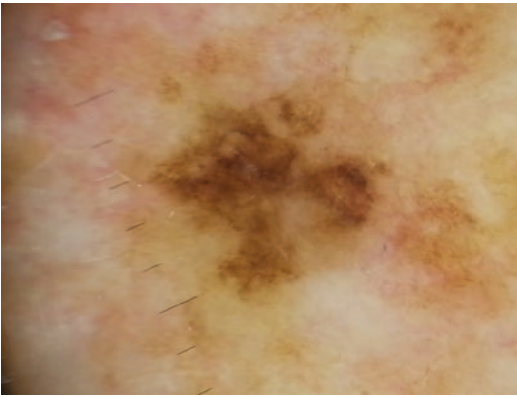
Fig. 56.36 Extrafacial lentigo malingnant melanoma

Melanoma with Special Characteristics

Melanoma in nonfacial chronically damaged skin: extrafacial LM.

Dermoscopic patterns seen in melanomas on nonfacial chronically sun-damaged skin are patchy peripheral pigmented island, angulated line pattern, structureless tan, and granularity pattern [55, 56] (Figs. 56.36 and 56.37).

Mucosal Melanoma

Early mucosal melanomas present brown-black macules with shades of gray. The diameter is larger than 1 cm and multifocal growth is possible. Advanced mucosal melanomas present as black or dark brown nodules com-

bined frequently with the macular part at the base of a tumor [35].

Mucosal melanoma has the following patterns: gray, white, or blue color plus structureless zones, irregular dots or globules, and atypical vessels [36].

Non-nodular Hypomelanotic Melanoma

These represent 2–8% of all melanomas and are an important diagnostic pitfall for clinicians. Any of the four subtypes of melanoma (superficial spreading, nodular, acrolentiginous, and LM) can occur as an amelanotic melanoma. To avoid missing it, a high index of suspicion is needed when evaluating isolated and persistent pink outlier lesions. From a dermoscopic perspective pure amelanotic melanomas reveal no pigment while hypomelanotic ones have subtle pigment, which is often present only focally. They present as symmetric erythematous macules and plaques with well-defined borders in 80% of the cases. Light-brown structureless areas have been associated with thin melanomas with a 93.8% positive predictive value. Melanomas with decreased or absent skin markings are significantly thicker than those with increased or normal skin markings [57].

It is important to consider amelanotic melanoma in the differential diagnosis of isolated and persistent erythematous outlier lesions, even if the lesion does not manifest any of the melanoma ABCD criteria [57].

How Reliable Is Dermoscopy and How Much Time is Needed to Perform it?

Our main objective is not to miss any skin cancer. The risk of missing a skin cancer in patients who are seen by a dermatologist for a localized problem (which does not involve examination of the whole cutaneous surface) is on the order of 1 in 50 patients, whereas the risk of missing a melanoma is about 1 in 400 patients [58]. With regard to dermatologists, a total body skin examination to all patients is recommended. Zalaudek et al. estimated that the time required to complete a total body skin examination with manual dermatoscopy was on the order of only 2–3 min [59].

Once examined clinically and by dermoscopy, patients will follow two distinct management paths, depending on their risk profile: (1) patients who have a single lesion or few lesions and (2) patients with multiple nevi. In the first group, if a lesion seems benign it may be left, but if it is suspicious it should be removed or monitored depending on the degree of suspicion. Monitoring is a specific procedure that helps reduce the number of unnecessary excisions in higher-risk patients, particularly those with multiple nevi. On the other hand, in low-risk patients with a single or a few slightly atypical melanocytic lesions, long term monitoring versus excision can be implemented. An alternative method to manage indeterminate or equivocal melanocytic lesions is short-term clinical and dermoscopic follow-up (2–4 months) [60].

Patients with multiple nevi should be on a monitoring program to ensure a comparative and analytic dermoscopic approach for early diagnosis of melanoma [60]. By this means the reduction in the number of unnecessary removals of benign lesions is around 75% [61]. The patient with multiple nevi should be included in a long-term clinical and dermoscopic monitoring program for the detection of subsequent melanoma [62, 63].

It is noteworthy that patient compliance is typically significantly higher for short-term (2–4 month) than longer-term (6–12 month) reviews [64].

Nonmelanocytic Lesions

As discussed earlier, the two-step dermoscopy algorithm allows the differentiation between melanocytic and nonmelanocytic lesions. Absence of melanocytic lesion criteria should lead us to think that we are facing a nonmelanocytic lesion and evaluate the presence of distinctive criteria of nonmelanocytic lesions.

Nonmelanocytic lesion criteria were described for SK, BCC, dermatofibroma, and vascular lesions (hemangioma and angiokeratoma). In this section, we revise these criteria with a brief description of clinical aspects.

Seborrheic Keratosis

SK is the most common benign epidermal tumor. Its importance lies in its high frequency and its similarity, in some cases, to malignant tumors such as BCC, SCC, and melanoma. SKs are more common in middle-aged individuals but they may also arise in adolescence. Its etiology is unknown. Genetic factors, sun exposure, and infections have been implicated as possible risk factors. Many patients with SK have a family history. Most lesions are asymptomatic, but itch and discomfort in friction areas are not uncommon. SK can appear in any topography except mucous membranes, palms, and soles [65].

The clinical presentation of SKs is polymorphous. They can present as macular, papular, polypoid, or cerebriform lesions, generally multiple and varied in size, usually between 2 to 20 mm in diameter. They have generally well-defined limits, as "stuck" on the skin surface, and may be warty, rough, or velvety. The color is very variable between beige, brown, brown-black, gray, and black with or without keratin cysts on the surface. SKs tend to persist and grow slowly over the years with no malignant potential [65] (Fig. 56.38).

Clinical polymorphism correlates with histologic subtype: acanthotic, hyperkeratotic, webbed, clonal, irritated, and melanoacanthoma. Some of these varieties can be melanoma simulators [65].
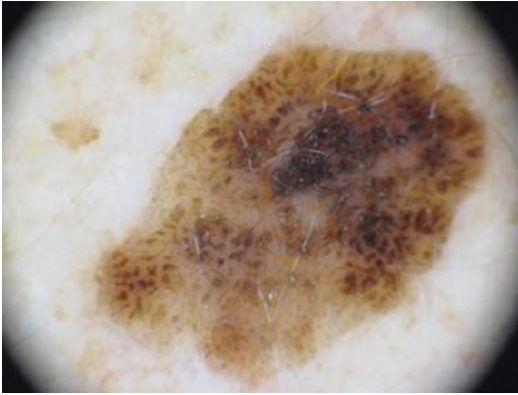
Fig. 56.38 Seborrheic keratosis: abrupt edges on the skin

Table 56.3 Dermoscopic criteria of seborrheic keratosis

Dermoscopic structures
Abrupt edge
Milia-like cysts
Comedo-like openings
Cracks and ridges
Hairpin vessels
Fingerprint-like structures

The first described dermoscopic features of SK were comedo-like openings and milia-like cysts. In 2001, the Dermoscopy Consensus NetMeeting defined more criteria for the diagnosis such as multiple milia, comedo-like openings, cracks and ridges (cerebriform aspect), and light-brown fingerprint structures [66]. In 2002, Braun et al. evaluated dermoscopic features of 203 pigmented SKs and added additional criteria such as cracks, hairpin vessels, demarcated borders, and moth-eaten edge. In addition, crypts, exophytic papillary structures, and the jelly sign were described, improving diagnostic sensitivity [66].

Dermatoscopic criteria of SK are listed in Table 56.3.

- Milia-like cysts: Yellowish white circular structures of 0.1–1 mm of diameter, present in 14–66% of SK [67]. Because milia-like cysts and comedo- like openings are less conspicuous with polarized dermoscopy, they blink when the observer toggles between light sources (nonpolarized and polarized), which are useful for identifying them [67–69]. SK

Fig. 56.39 Seborrheic keratosis. *Red*: milia-like cysts. *Yellow*: comedo-like openings. *Blue*: abrupt edges
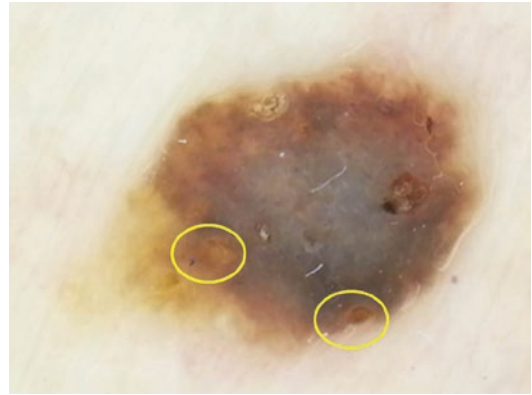
Fig. 56.40 Seborrheic keratosis. *Yellow*: comedo-like openings

can be also observed in melanocytic lesions, congenital melanocytic nevi, and in some melanomas [67, 68] (Fig. 56.39).
- Comedo-like openings: Circular structures similar to a comedo, light or dark brown, yellowish, or black in color. They are observed in 71–80% of SKs and can be also present in papillomatous nevi [67, 69–71] (Figs. 56.39 and 56.40).
- Cracks and ridges: These have the same meaning. The former are described as linear depressions that resemble brain surface. The latter are hypo- or hyperpigmented and resemble "fat fingers" [69, 70] (Fig. 56.41).
- Hairpin vessels: Elongated looped vessels at the periphery of the lesion, regularly distributed, with monomorphic appearance and usu-
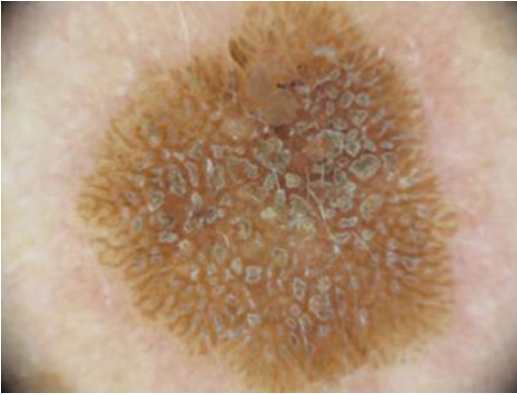
Fig. 56.41 Seborrheic keratosis: cracks (*blue*) and ridges (*red*)
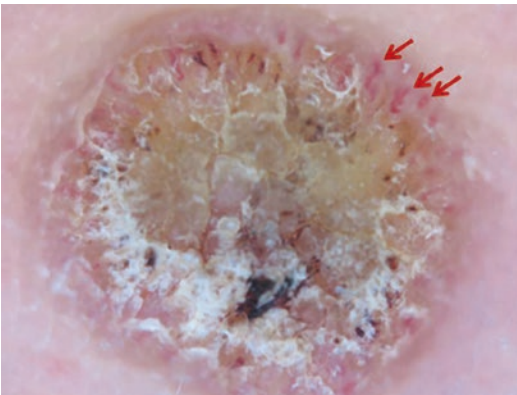
Fig. 56.42 Irritated seborrheic keratosis. *Red*: hairpin vessels with *white* halo

ally surrounded by a whitish halo, which is a keratinization sign. They are usually present in head and neck lesions [67, 69–71]. In irritated SK, hairpin vessels are irregular, polymorphous, elongated, twisted, or double-stranded and different in size, simulating melanomas. They are present in 63% of SKs and in 94% of irritated SKs [67] (Fig. 56.42).

- Fingerprint-like structures: Dark-brown, fine parallel cord-like structures characteristically seen in the periphery of SK and solar lentigo [69–71]. These structures are present in 55–100% of plane SKs [67].
- Treatment of SK is not necessary. They are usually treated for cosmetic purposes or when symptoms appear. Among therapeutic options

there are different destructive methods such as cryotherapy, electrodesiccation with curettage, or laser ablation, which are very effective. Most common complications include depigmentation, scarring, and recurrence as a consequence of incomplete excision [65].

Basal Cell Carcinoma

BCC is a primary malignant epithelial skin tumor derived from immature stem cells of the basal layer of the epidermis and its annexes. BCC grows slowly, in close relationship with the surrounding stroma, with minimal metastatic potential [72].

BCC is the most common cancer in humans. Its incidence has been increasing at a rate of 4–8% annually since 1960 [73].

It produces considerable morbidity although its death rate is low [74].

Clinically, nodular BCC is the most common variant. Its presents in the head and neck, posing as a nodule or smooth papule, solitary, erythematous, translucent, shiny, and pearlescent, showing telangiectasia on its surface [72, 74, 75]. Ulceration of the lesion is common as well as pigmentation (named pigmented BCC) [76].

Superficial BCC presents as a flat erythematous scaly patch or papule, well defined in shape, with slow centrifugal growth, most often located in the trunk [72, 74, 77]. Dermoscopy has been extensively described for nodular and superficial BCC.

Dermoscopic criteria for BCC are as follows [78] (Table 56.4).

- Leaf-like areas: Gray, brown or blue, shiny, discrete bulbous structures that resemble a maple leaf. They are seen on the edges of pigmented BCC [69]. Leaf-like areas show a 100% specificity and 20% sensitivity for the diagnosis of pigmented BCC [71] (Fig. 56.43).
- Spoke wheel structures: Radially arranged [69, 71, 79] projections with a more pigmented brown, blue, or gray center. They are seen in 10% of cases and have a specificity of 100% [70, 80] (Fig. 56.43).

Table 56.4 Dermoscopic criteria of basal cell carcinoma

Classic criteria	New criteria
Leaf-like areas	Concentric structures
Spoke wheel structures	Multiple blue-gray focused points
Multiple blue-gray globules	Crystalline structures
Large blue-gray ovoid nests or blotches	Thin and short superficial telangiectasia
Linear and arborizing (branch-like) telangiectasia	Multiple small erosions
Single or multiple ulceration	

Fig. 56.44 *Black arrows*: multiple blue-gray globules. *Red arrows*: ulceration

Fig. 56.43 Basal cell carcinoma. *Red*: leaf-like areas. *Yellow*: spoke wheel structures

Fig. 56.45 Basal cell carcinoma: linear and arborizing (branch-like) telangiectasia

- Multiple blue-gray globules: Circular blue or gray structures. They can appear as the unique diagnostic clue for pigmented BCC [69, 70]. Multiple blue-gray globules are present in 27% of pigmented BCC with 87% specificity for diagnosis [79] (Fig. 56.44).
- Large blue-gray ovoid nests or blotches: Round or ovoid formations larger than globules, homogeneously bluish [69–71]. They are present in more than half of the cases of pigmented BCC, with 97% specificity [79].
- Linear and arborizing (branch-like) telangiectasia: Thick- and thin-branched vessels. This may be the unique criterion of unpigmented BCC [69, 70, 79]. These vessels are present in more than half of the cases and in 90% of

superficial BCCs. Its specificity is 77% [79] (Figs. 56.45 and 56.46).
- Single or multiple ulceration: Areas with interruption of the epidermis that show a sero-hematic orange or yellow crust in its surface. Ulceration of a BCC may occur early, unlike melanoma where this is usually a late event [71] (Fig. 56.44).

Nonclassical criteria of BCC were latterly described. These are present in 26% of cases and include the following structures [78]:

- Concentric structures: Similar to globules, irregularly shaped, blue, gray, or brown with a darker central area. They may represent the
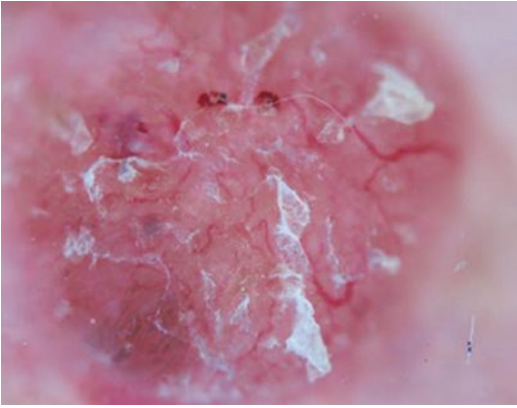
Fig. 56.46 Basal cell carcinoma: linear and arborizing (branch-like) telangiectasia
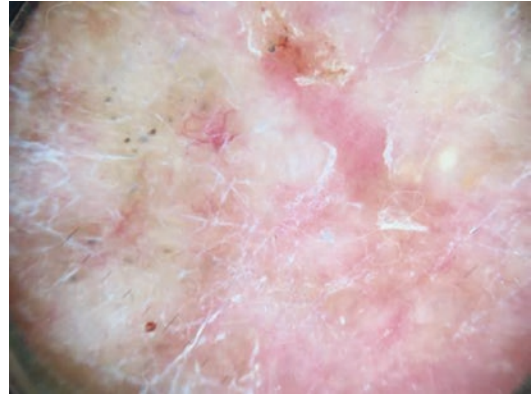
Fig. 56.48 Basal cell carcinoma. *Red*: multiple blue-gray focused points
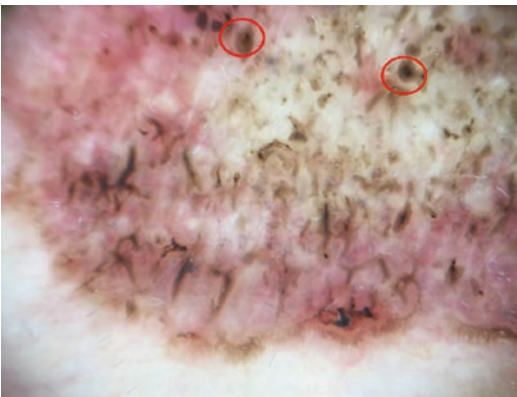
Fig. 56.47 Basal cell carcinoma. *Red*: concentric structures
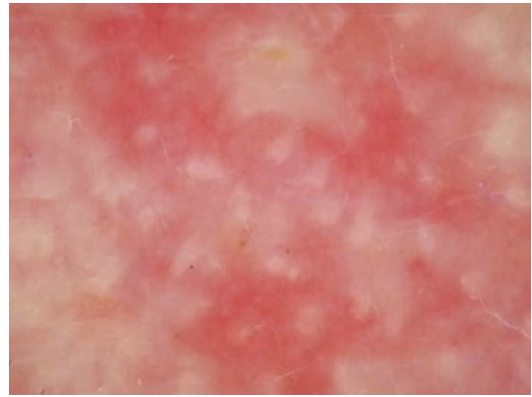
Fig. 56.49 Basal cell carcinoma: thin and short superficial telangiectasia

early stage of spoke wheel structures. They are present in 7.6% of BCCs [78, 81] (Fig. 56.47).

- Multiple blue-gray focused points: It is postulated that they would be the initial form of the blue-gray globules; they are present in 5% of BCCs [78, 81] (Fig. 56.48).
- Bright white-red areas: Areas without structures, pink or pearly, present in 100% of the superficial BCCs [78].
- Crystalline structures: Short, thick and shiny, pearly whitish lines due to the presence of collagen bundles in thickened dermis. These structures are only visible with polarized light dermoscopy. They can also be seen in dermatofibromas, scars, Spitz nevi, and melanomas [47, 78, 80, 82].
- Thin and short superficial telangiectasia: Also known as microarborizing vessels. They are

telangiectasias with a smaller caliber than 1 mm with little or no ramifications. They are present in more of the 91% of superficial BCCs and are considered the initial form of branched vessels [78] (Fig. 56.49).
- Multiple small erosions: Erosions of less than 1 mm in diameter, reddish-brown in color. They adopt a peripheral distribution in the lesion with a frequency of 8.5–70% in superficial BCCs [78] (Fig. 56.50).

Treatment options for BCC are beyond the scope of this chapter and are discussed in Chap. 15.

Dermatofibroma

Dermatofibroma, or superficial benign fibrous histiocytoma, is a common benign tumor, more
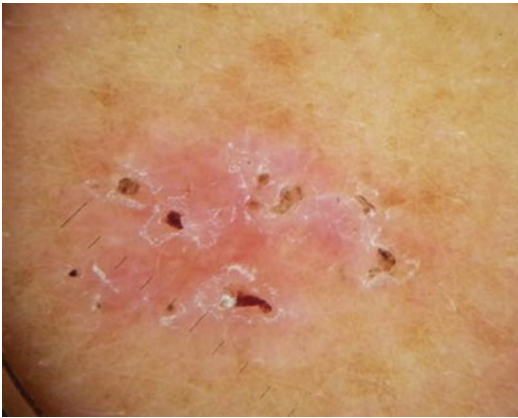
Fig. 56.50 Superficial basal cell carcinoma: multiple small erosions

Table 56.5 Dermoscopic criteria of dermatofibroma [83]

Pattern 1: Total delicate pigment network
Pattern 2: Peripheral delicate pigment network and central white scar-like patch
Pattern 3: Peripheral delicate pigment network and central white network
Pattern 4: Peripheral delicate pigment network and central homogeneous area
Pattern 5: Total white network
Pattern 6: Total homogeneous area
Pattern 7: Total white scar-like patch/multiple white scar-like patches
Pattern 8: Peripheral homogeneous area and central white scar-like patch
Pattern 9: Peripheral homogeneous area and central white network
Pattern 10: Atypical pattern

Fig. 56.51 Dermatofibroma: peripheral delicate pigmented network and central white scar-like patch (pattern 2)

frequently located in the lower extremities of young females, but not exclusively. Clinically it presents as a papule or firm nodule with smooth surface in shades of brown. It can be unique or multiple. The pinch test is helpful and easy for diagnosis, and consists of squeezing the lesion from the sides, resulting in dimpling of overlying skin [83].

The most frequent dermoscopic feature is the presence of a fine peripheral pigmented network and a white central scar-like patch (Fig. 56.51) [69, 70]. In 2008 Zaballos et al. described ten different dermoscopic patterns for dermatofibroma [83] (Table 56.5, Figs. 56.51, 56.52, and 56.53).

Atypical patterns can often be difficult to differentiate from melanocytic lesions including melanoma (Fig. 56.54) [84]. Many histopathologic variants have been described. Surgical excision should be performed in high-risk patients who present with changes in the lesion [85].

In 2013 Ferrari et al. described a group of dermatofibromas showing a pattern of atypical lesions as "nondermatofibroma-like patterns", including melanoma-like, vascular tumor-like, BCC-like, tumor-like collision, and psoriasis-like [85].

A significant association between the pattern of melanoma-like dermatofibroma and the histopathologic variant hemosiderotic/aneurysmal was found. This shows in dermoscopy a multicomponent pattern with a homogeneous bluish-red central area. The histologic correlation in these central structures is the presence of intra- and extracellular spaces filled with blood and hemosiderin deposits [84].

Vascular Lesions: Hemangioma and Angiokeratoma

Capillary hemangiomas are common skin tumors that can appear as single or multiple lesions. Clinically they present as macules or papules that vary in size, characterized by bright red or purple color. The diagnosis is usually clinical, but often

Pattern 1	Total delicate pigment network
Pattern 2	Peripheral delicate pigment network and central white scarlike patch
Pattern 3	Peripheral delicate pigment network and central white network
Pattern 4	Peripheral delicate pigment network and central homogeneous area
Pattern 5	Total white network
Pattern 6	Total homogeneous area
Pattern 7	Total white scarlike patch/multiple white scarlike patches
Pattern 8	Peripheral homogeneous area and central white scarlike patch
Pattern 9	Peripheral homogeneous area and central white network
Pattern 10	Atypical pattern

Fig. 56.52 Dermoscopic patterns of dermatofibroma (Modified from Zaballos et al. [83])
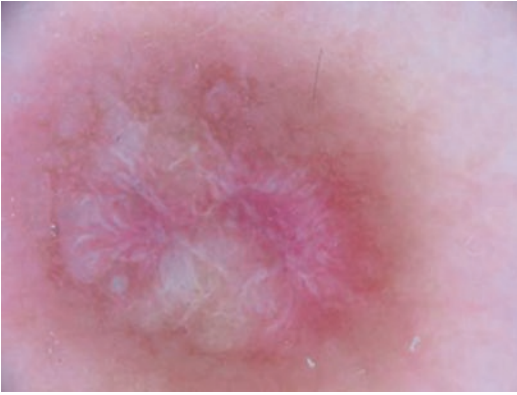
Fig. 56.53 Dermatofibroma: total white network (pattern 5)
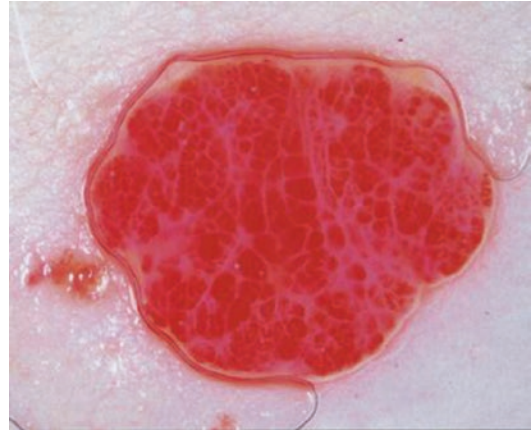
Fig. 56.55 Hemangioma: red lagoons
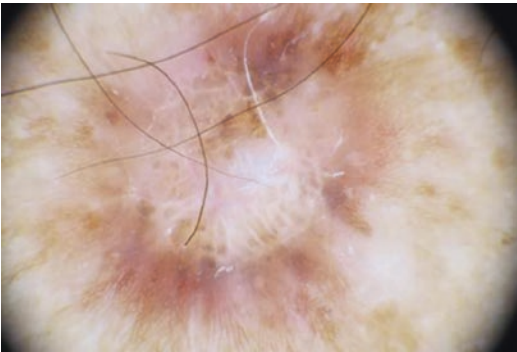
Fig. 56.54 Dermatofibroma: atypical pattern (pattern 10)
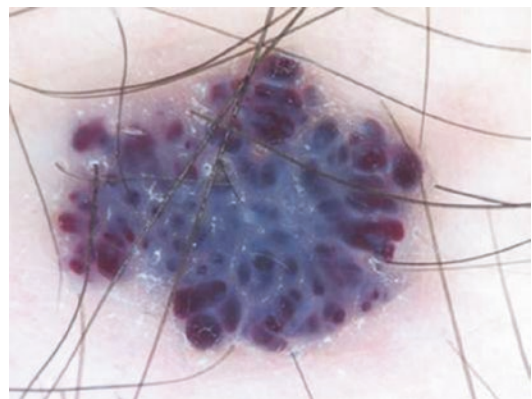
Fig. 56.56 Angiokeratoma: vascular lagoons and hyperkeratosis covering the lesion like a veil

can simulate a nodular melanoma or metastatic melanoma, and it is in these cases is where dermoscopy is useful [69].

Dermoscopic features are the presence of red lagoons which could show bluish-red or black color, posing as well-defined structures, circular or ovoid, which vary in size and color within the same lesion [70–72]. These criteria have a sensitivity of 83.9% and specificity of 99.1% for the diagnosis [86] (Fig. 56.55).

Angiokeratomas are vascular malformations that clinically appear as dark-red to blue-black lesions, single or multiple, and circumscribed [24]. They consist in the combination of vascular ectasia with hyperkeratosis [69].

Angiokeratomas have five clinical presentations: single or multiple lesions, circumscribed, Fordyce angiokeratomas, angiokeratomas of Mibelli, and diffusum corporis [87].

Dermoscopy shows the presence of dark red-blue lagoons and white veil with peripheral erythema that may have a bleeding scab [87] (Fig. 56.56).

Lagoons in angiokeratomas tend to be less defined than that those of hemangiomas. Hyperkeratosis covering the lesion with yellowish white coloring is observed. In early lesions the differentiation between hemangioma and angiokeratoma may be difficult [70].

Often angiokeratomas pose differential diagnosis with other pigmented lesions such as melanocytic nevi, Spitz nevi, melanoma, BCC, SK, and other benign vascular lesions such as pyogenic granuloma. Dermoscopy is useful to define the diagnosis when it shows characteristic red-bluish lagoons with white veil covering the lesion [87].

Actinic Keratosis

AK is considered to be an in situ epidermal dysplasia that frequently develops on chronic sun-damaged skin [88–90]. Its main clinical and management aspects are discussed in Chap. 14.

The diagnosis of AK is usually simple, with no need of histologic evaluation, and is based on its typical clinical appearance of nonpigmented, circumscribed, rough and scaly reddish papule or plaque located in a photodamaged site such as the face, lower neck, and back of hands [89, 91]. Less frequently it can be pigmented, making the differential diagnosis with melanoma difficult (or even impossible) [89]. Most AKs are asymptomatic and rarely develop as solitary tumors [91, 92].

The diagnostic sensitivity and specificity of dermoscopy for classical AK has been reported to reach 98% and 95%, respectively, with a high level of concordance between this technique and histopathology [88, 93]. Four dermoscopic criteria have been established, and a similar pattern is seen in each individual for different AKs [88, 92].

Classical Nonpigmented Actinic Keratosis

According to Zalaudek et al., three different grades are described [93].

- Grade 1: When the AK is a slightly palpable lesion (better felt than seen) and exhibits a pink to red pseudonetwork pattern surrounding hair follicles and discrete white to yellow scale upon dermoscopy [88, 93] (Fig. 56.57).
- Grade 2: Refers to a moderately thick lesion that is easily felt and seen. This lesion is dermoscopically typified by an erythematous
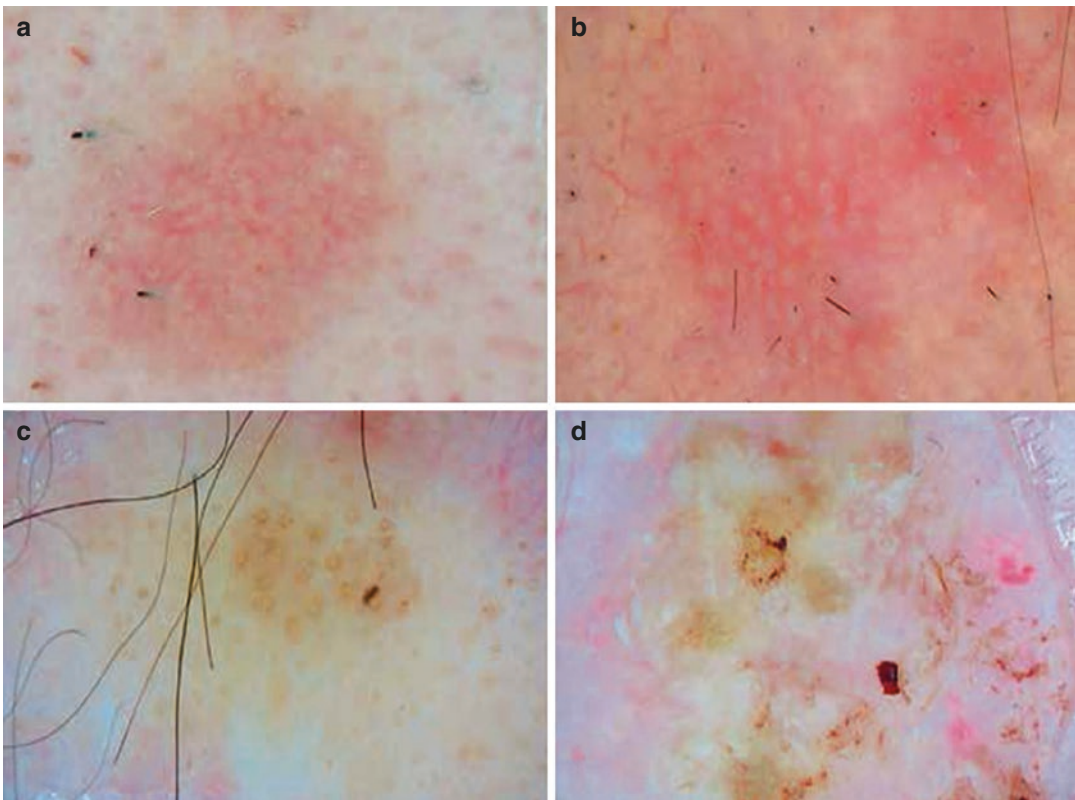
Fig. 56.57 Nonpigmented actinic keratosis (**a**) grade 1: red pseudonetwork; (**b**) grade 2: "strawberry pattern"; (**c**, **d**) grade 3: hyperkeratosis and enlarged follicular openings filled with keratotic plugs over a scaly and white to yellow appearing background or a structureless area

pseudonetwork that is intermingled with white to yellow, hyperkeratotic, partially confluent, and enlarged follicular openings surrounded by white halo (targetoid appearance). It is called a "strawberry pattern" and is seen in 95% of AKs [12, 88, 92, 93]. Of note, the term "strawberry pattern" is a metaphorical term that sticks in the memory and represents a useful diagnostic clue [94] Fig. 56.57.

- Grade 3: When the AK is very thick, hyperkeratotic, and can exhibit by dermoscopy either enlarged follicular openings filled with keratotic plugs over a scaly and white to yellow appearing background, or a structureless area [93] (Fig. 56.57).

Last but not least, bowenoid AK is an infrequent type of AK that exhibits a vascular pattern shown by regularly distributed glomerular vessels with no clustering arrangement as seen in classic Bowen disease [12, 95].

Pigmented Actinic Keratosis

Owing to the overlapping of clinical and dermoscopy patterns with LM, the diagnostic sensitivity and specificity for pigmented AK is much lower than that for nonpigmented AK.

Classically, pigmented AK shows a superficial, broken pseudonetwork consisting of brown, curved double lines that surround enlarged, partially confluent, hyperkeratotic follicles of various sizes. Scales can be associated [89, 92, 93]. A feature typically described for solar lentigo and seborrheic keratosis, such as the moth-eaten border, has been reported for pigmented AK [92].

In addition, pigmented AK may sometimes reveal pigmented structures that overlap with those of LM. These structures include annular granular pattern (multiple grayish-brown dots and globules which coalesce around hair follicles), rhomboidal structures around the follicular openings, and asymmetric, pigmented follicular openings. In such cases, a biopsy is mandatory to rule out LM [89, 92, 93] (Fig. 56.58).
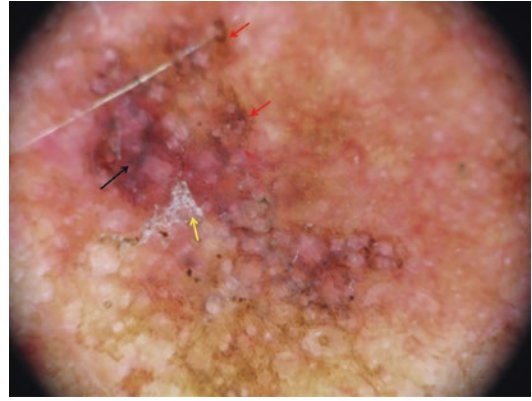
Fig. 56.58 Pigmented actinic keratosis: hyperkeratosis, scale (*yellow arrow*), rhomboidal structures (*black arrow*), and pigmented follicular openings

Other Frequent Uses of Dermoscopy

Common Daily Uses for Infections

Four parameters should be assessed when applying dermoscopy in the realm of inflammatory and infectious diseases: (i) morphologic vascular patterns; (ii) arrangement of vascular structures; (iii) colors; and (iv) follicular abnormalities. The presence of other specific features should also be evaluated [96].

Molluscum Contagiosum

The diagnosis of molluscum contagiosum, a common skin viral infection of the epidermal keratinocytes caused by a poxvirus, is generally easy because of its characteristic cutaneous feature of umbilicated translucent papules [97–99]. Lesions are generally numerous, characteristically of 2–4 mm diameter, with glossy appearance [99].

In adults it may raise diagnostic doubts when it presents as a single lesion or when the lesion is inflamed. In locations such as the face, molluscum can be mistaken for BCC, sebaceous hyperplasia, or other adnexal tumor [100]. Dermoscopy may facilitate the clinical diagnosis [99].

Molluscum contagiosum shows a characteristic dermoscopy pattern consisting of a central polylobular white to yellow amorphous structure
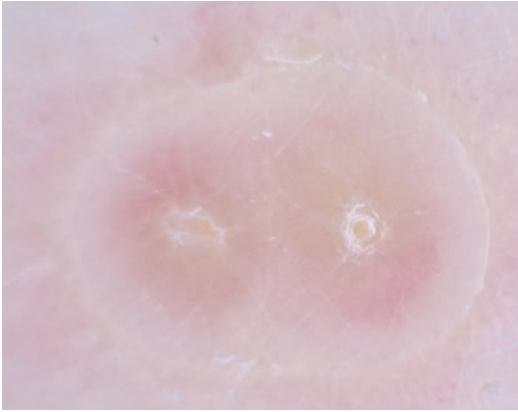
Fig. 56.59 Molluscum contagiosum showing a skin-colored surface with a central white to yellow amorphous structure

(Fig. 56.59) [95]. The hallmark dermoscopic pattern is crown vessels at the periphery of the lesion with a radial distribution (not crossing the center of the lesion) that resembles a red crown [95, 98, 99]. These crown vessels are also described for sebaceous hyperplasia. Other frequent dermoscopy findings are a whitish peripheral halo and hyperkeratosis [95].

In 2011 a study conducted on dermoscopy of 211 lesions of molluscum contagiosum led to a further vascular pattern being described: the punctiform vascular pattern. This consists of small reddish dots inside the lesion (also described in melanoma, clear cell acanthoma, lichen planus, and eccrine poroma, among others). The punctiform pattern prevails in inflamed and/or excoriated lesions and in lesions with perilesional eczema [98].

Warts

Cutaneous and mucosal viral infections due to human papillomavirus are extremely common in clinical practice. The diagnosis is generally easy in all its clinical forms: common warts, flat warts, filiform warts, plantar warts, and genital warts. However, in some cases the diagnosis may be challenging, as it occurs in traumatized and irritated lesions or those previously treated [100].

Dermoscopy has been demonstrated to be a valuable tool in these infections, both for diagnosis and monitoring treatment [95, 98].

Common warts display a whitish halo that corresponds to dense papillomatosis, each containing a central red dot [95, 98, 100]. The halo may not be visible if there is significant vascular occlusion. This vascular pattern is described as multiple homogeneous but with nonspecific distribution of dots, ranging in color from red to black [100]. Black dots indicate thrombosed vessels [95]. Plantar warts show more prominent hemorrhages and black lines corresponding to thrombosed capillaries and microbleeds caused by trauma from ambulation. The identification of the aforementioned structures in hyperkeratotic plantar lesions helps to distinguish warts from common conditions such as calluses and corns [95, 98].

Flat warts exhibit small dotted vessels with regular distribution on a yellowish brown background [98, 100] (Fig. 56.60).

Genital warts, also known as condylomas, show a mosaic pattern consisting of a white reticular network surrounding central small islands of unaffected mucosal skin [98]. Higher magnification demonstrates that those islands correspond to a vascular pattern, given by many punctate (dotted vessels) and/or red globules (bigger vessels) [100, 101]. Dermoscopy in genital warts can be useful to differentiate them from vestibular papillae and pearly penile papules, normal features of female and male external genitalia, respectively [98].
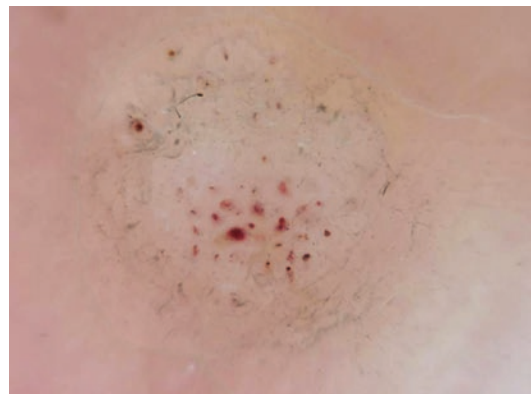
Fig. 56.60 Vulgar wart showing homogeneously distributed dots, from red to violet, and hemorrhages. Whitish peripheral halo

Squamous Cell Carcinoma

In the field of SCC a progression model has been described, and alongside it specific dermoscopic patterns associated with different stages of progression have been identified. Dermoscopy findings allow the differentiation between AK, intraepidermal carcinoma (IEC) also commonly named Bowen's disease or SCC in situ, and invasive SCC [93, 102].

Intraepidermal Squamous Cell Carcinoma or In Situ Squamous Cell Carcinoma

Dermoscopy exhibits classically dotted/glomerular vessels arranged in small clusters and discrete yellowish or white opaque scales, representing hyperkeratosis [13, 102]. Both dotted and glomerular vessels are frequently seen in the same lesion [13].

Invasive Squamous Cell Carcinoma

SCC shows highly polymorphous vascular structures [13, 95]. The prevailing ones are elongated, linear vessels and/or hairpin vessels of varying shape and distribution, without grouping into clusters. In addition to vascular patterns, signs of keratinization (representing further important clues for diagnosis) are usually seen as white structureless amorphous areas, a central mass of keratin, or, less frequently, targetoid appearance follicular openings consisting of an opaque, yellow center surrounded by a white halo (white circles). Variable areas of ulceration are often seen [13, 93, 95, 102].

Keratoacanthoma

Keratoacanthoma is actually regarded as a variant of SCC due to its resemblance to the histopathology of SCC [13].

The most stereotypical dermoscopic pattern is typified by a central amorphous, structureless whitish mass of keratin, which is surrounded by elongated telangiectasias of large caliber and few branches [13, 93, 102]. These large-caliber vessels may be sometimes mistaken for the arborizing vessels of BCC; however, they are less focused, with fewer branches, and are frequently associated with signs of keratinization [93, 102].

Future Perspectives

Future perspectives for dermoscopy are enormous.

It now has an increasing role in the recognition of several inflammatory and infectious diseases, as well as their discrimination from skin tumors [96].

Moreover, recent data indicate that it might also be worthwhile for the assessment of the outcome and adverse effects of various treatments [103].

Dermoscopy is also a promising bridge connecting clinical with basic molecular research in dermato-oncology [104]. A correlation between an individual genetic status and dermoscopy patterns of nevi and melanoma can be made. For example, melanomas with BRAF V600E mutation or NRAS mutations reveal dermoscopic signs of regression at higher frequency compared with melanoma, which are wild-type for these mutations [105, 106].

Dermoscopy will also be a link between new technologies and clinical practice. Likewise, dermoscopy and reflectance confocal microscopy represent complementary/synergistic methods for the evaluation of skin tumors [107].

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Teledermatology

57

Daniel Holthausen Nunes

Key Points
- Teledermatology is a new tool that bridges the distance between the dermatologist and remote areas
- Teledermatology aims to screen severe cases and support to general physicians
- The effectiveness of teledermatology is greater if the photos obtained are systematic and follow specific protocols.
- There is a considerable reduction in costs of referral flow with the implementation of teledermatology, especially in countries where the health system is public or distribution of specialists is uneven.

Introduction

Dermatology is one of the most visual specialties in medicine and is also suited for modern telemedicine techniques. It is not difficult to see the potential for telemedicine to be widely disseminated. Since dermatology is the field of medicine responsible for the care of the skin and its appendages, it is often possible to make a diagnosis, with due respect to the patient's medical history, through images/pictures and visualization of the lesions [1].

Teledermatology refers to the delivery of dermatologic care via information and communication technology [2]. Thus, it can be said that teledermatology represents the field of telemedicine that aims to apply new communication and information technologies to dermatologic practices in order to reduce the need for the patient and the specialist to meet face to face, with a view toward ensuring effective health planning, research, education, clinical discussion, second opinion, and expert dermatologic care. Given the strong visual component of dermatology as a specialty it has a significant benefit for the use of telemedicine, whose basic function is remote diagnostics—in other words, health care at a distance [1, 3–6].

In teledermatology, dermatologists use telemedicine techniques to diagnose and treat patients from a distance, which involves the clinical evaluation of skin lesions and the review of laboratory findings. The primary aim is to ensure that patients from remote areas receive specialized dermatologic care. Other aims are to decrease the number of hospital visits and increase diagnostic efficiency. One objective of teledermatology is to deliver

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high-quality healthcare more efficiently by moving a patient's information rather than moving the actual patient [7, 8].

The merit of teledermatology was aptly described as follows: "teledermatology makes three promises: better, cheaper, and faster dermatologic care." "Better" quality is achieved by reliance on sophisticated devices for remote diagnosis and by extending the reach of dermatologists to serve patients in need of a specialist. "Cheaper and faster" are achieved by improved efficiency from increased volumes of patients, as well as "avoiding unnecessary and time-consuming face-to-face appointments" [9].

Thus, we have as a means, through telemedicine and teledermatology, to gain a second formative opinion that can be defined as the search for and delivery of medical information from a trained professional when distance no longer constitutes a barrier. Moreover, the second formative opinion has as one of its greatest benefits assisting the applicant in identifying the professional health problem and the therapeutic strategy [10, 11].

Two modalities of exchange of information in telediagnostics can be used in gaining the second formative opinion: synchronous mode (real-time), whereby the third party and the applicant, with the patient, participate in a real-time query; and asynchronous mode (store and forward), whereby the question is transported to a database and subjected to further consultation [12].

State of the Art

Nowadays telediagnosis, specifically in dermatology, lacks clear regulation, unlike other specialties that already have such specific protocols contemplated as an established procedure. In dermatology, perhaps because of easy access to the patient's own skin lesions and technology (digital photography, computers, and smartphones), the boundaries between the ideal and the actual are cloudy, besides being ethically prohibited [13].

The possibility of having a remote diagnostics service can ultimately end "consultations" by emails/social networks, including formalizing fees. It is important to clarify that this interaction should always be "medical doctor–specialist–medical doctor" and not directly between the specialist and the patient. However, this point is subject to an extensive discussion of responsibility around the medical act itself. In this case, the specialist accepts unlimited liability for any risks he/she undertakes [14].

We should bear in mind that face-to-face consultation remains the gold standard for diagnosis; and while the aim of teledermatology is to achieve the quality of this reference standard, the conventional service should be maintained as long as the resources and conditions for offering it are available. It is impossible to properly manage a disease without a precise diagnosis [15].

Some models of teleconsulting, such as second formative opinion and tele-education, often occur between peers, with clarification of intent on specific questions, theoretical basis or continuing education, respectively. In this regard, the sooner we define and establish rules, the lower will be the risk of incurring serious ethical shortcomings by omission or negligence. The use of social networks, such as Facebook or WhatsApp, which are excellent in function for homogeneous groups, are not ideal discussion forums because of, for example, patient exposure.

Some patients themselves search the Internet to seek further information or advice regarding their illness. Patients are connecting to databases or emailing their physicians for more advice. However, patients obtaining advice by using the Internet may increase their level of anxiety or reach false conclusions, which may lead to poor outcome [16].

Telediagnosis thus aims to include the mandatory requirement of (1) a specialist who is responsible for providing a report (diagnosis), based on relevant clinical information provided by the physician, and (2) good-quality images. Owing to the large number of dermatologic diseases and their clinical and chronologic variability and difficulty in standardizing photos, the creation of specific protocols and tools is essential for enabling remote diagnostics in dermatology [10, 12, 17]. The method, as employed for example in the second formative

opinion, should be asynchronous; however, the program can be developed via the technology to enable a dialogue between professionals simultaneously and synchronously in specific and selected cases [18, 19].

Teledermatology relies on the use of electronic devices to capture, transfer, and process information gathered by remote providers, typically general practitioners (GPs). It can be conducted in either synchronous fashion (with patient and provider interacting in real time) or asynchronously. The latter, also referred to as "store-and-forward" (S&F) modality, is often preferred by providers for convenience, better workflow, and greater efficiency. Because skin disorders all manifest on the surface of the body, digital photography is the most common tool for capturing diagnostic information, as a substitute for visualization and touch. Other devices include dermoscopes (surface contact microscopes that provide high-resolution images) and ex vivo confocal laser microscopy (an optical imaging technique for increasing optical resolution and contrast to eliminate out-of-focus light). Clinical notes and observations also constitute important sources of information.

The teledermatology process is based on photography, dermoscopy, or newer technologies (confocal microscopy), and consists of three basic models: (1) primary teledermatology, or direct service for patients for initial diagnosis and referral; (2) secondary teledermatology, or service for primary care providers for consults and triage; and (3) tertiary teledermatology, or specialist-to-specialist consults [9].

Currently it is difficult not to notice that one of the impediments to the achievement of a comprehensive and effective health system is the collision with economic restrictions. In this sense, the second formative opinion and remote diagnostics introduce alternatives to overcome this barrier, since these are procedures that are inexpensive in relation to their concrete results [20–27].

Another notable fact is the geographic maldistribution of physicians [23, 28]. Most specialists, for several reasons, prefer the large urban centers and tend to stay on the outskirts of urban centers, leaving outlying areas under the responsibility of often less skilled professionals. Remote diagnostics in dermatology enables the assessment of patients by a medical expert distant from the home, preventing the possibility of delay in simple treatments because of the distance between patient and expert. In addition, this new technique of exchanging information enables appropriate treatment for residents of remote regions [1, 3, 13, 20, 27].

It is true that an accurate diagnosis is the precursor of a successful therapeutic intervention; however, the dynamics of medicine as well as the various ways in which a dermatologic disease can manifest interferes in the skill of clinical judgment. Given this reality, coupled with the aforementioned economic and geographic factors, the remote diagnostics teledermatology looms large as an innovative method of assistance to professionals and a facilitator of proper access to healthcare.

Four factors that may account for a successful teledermatology program have been identified : (1) preselection of patients, (2) image quality, (3) dermoscopy for pigmented lesions, and (4) an effective culture and infrastructure. Three of these four critical factors for teledermatology programs should be implemented in any teledermatology system: first, preselection of patients; second, quality clinical photographs; and third, quality dermoscopic photographs of potentially malignant lesions. Any system planning to start a teledermatology service must anticipate that there can be a steep learning curve for the referring providers and imagers. It is crucial to establish training and standardized guidelines for referring providers and teleimagers and to facilitate continuous feedback among referrers, imagers, and readers [9].

The development of specific protocols and guidelines should be used to familiarize the GPs about the methods and procedures, such as for skin cancers (melanoma and nonmelanoma), psoriasis (severe), and leprosy, facilitating access of the patients to specialized clinics, creating the culture and the need for teledermatology for other skin diseases. In this way, a generic protocol can be used for remote diagnostics in dermatology with risk classification, making an appointment for a face-to-face consultation with a specialist easier and faster [29].

The fourth identified factor, culture and infrastructure, directly affects teledermatology success but is not as easy to implement in all programs. The capacity of primary doctors to participate effectively in teledermatology, either because of attitude or resources, plays a crucial role in the success of teledermatology programs. This issue must be addressed particularly when planning expansion of a successful teledermatology pilot program, as the larger pool of primary care providers may not have the enthusiasm of the pilot participants, for a variety of reasons, e.g., already feeling overburdened, lack of interest in technology, or other competing demands.

Some procedures can increase the effectiveness of teledermatology.

During conventional face-to-face consultation with the GP in a primary health unit the relevant patient data is entered on a virtual platform, which allows referral to the specialist when needed. Indications of all patients who show signs or symptoms of skin disease for whom the treating physician deems referral to the specialist necessary are forwarded.

The patient selected for consultation with dermatologist is then requested to undergo the examination, where agreement to the collection and holding of data is granted by signing the free and informed consent form.

The photographic record for the investigation of suspected cases is carried out following a protocol consisting of three steps: a panoramic photo, a close-up photo with scale, and a photo contact/dermatoscopy in cases of suspicion of skin cancer [30] (Fig. 57.1).
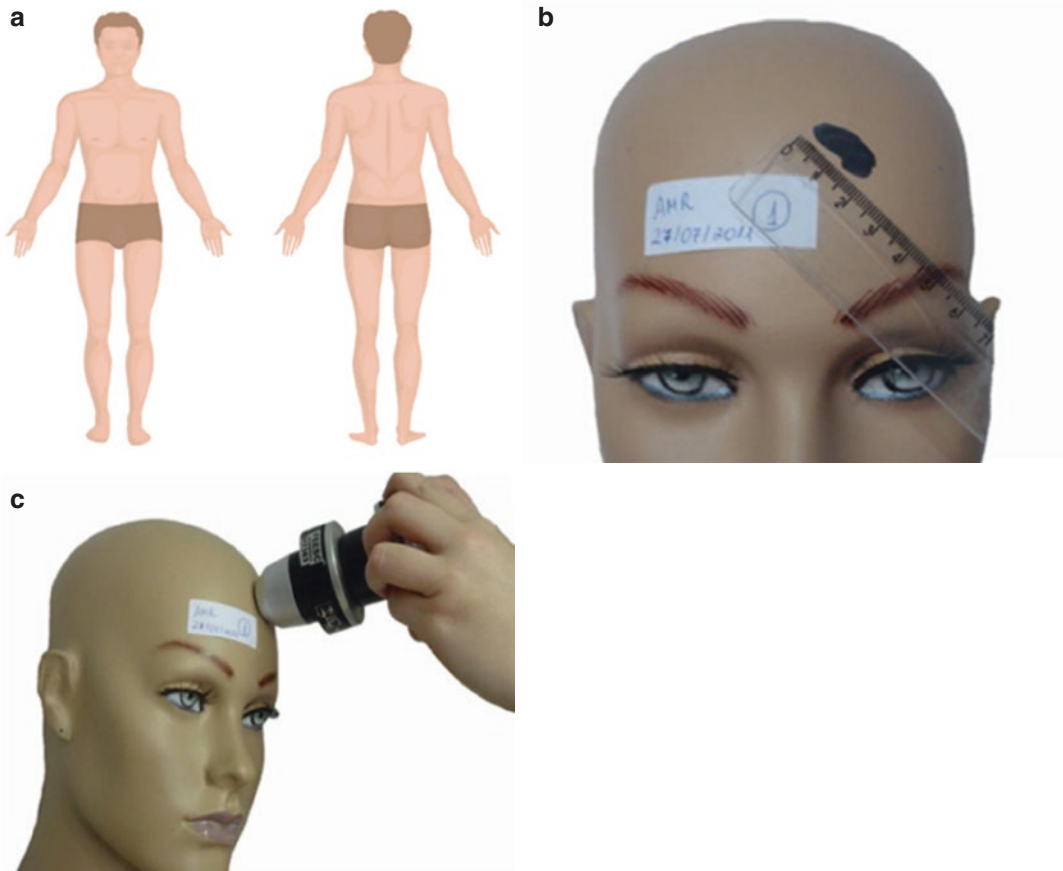
Fig. 57.1 Photo acquisition protocol. (**a**) Panoramic photo. (**b**) Close-up photo. (**c**) Dermoscopy

Regarding the panoramic photo, the technician is advised to identify each injury, using a label with date, initials of the patient, and lesion number, in order to create a panoramic image of the body region (head, torso, arms and legs, may be front or back) affected by one or more lesions. At this stage, the technician is advised not to use the zoom mode [30].

At the second stage, the close-up photo with scale, the technician is instructed to shoot at a distance of about 30 cm from the injury without the use of a zoom function, and to place a scale parallel to the injury to serve as reference to the actual size of the lesion.

Finally, the third photo is taken using dermoscopy. The dermatoscope is connected to the digital camera. The technician applies gel on the lens of the camera and photographs each lesion by using the dermatoscope placed against the patient's skin and maximizing the zoom level.

After collection, the data are transmitted through an internet environment developed exclusively for sending data corresponding to each patient. Whenever a new case is loaded into the portal, the examinations are available for an evaluation report by the dermatologist and can be accessed through a restricted site.

All reports are published in a structured and standardized way, obligatorily consisting of the description of the study, primary elementary lesion, secondary lesion, color, morphology, size, location, and distribution. The report concludes with the compatibility of diagnosis (medical assistant) with the remote diagnostics (dermatologist), whereby another hypothesis may be suggested according to the interpretation of clinical data and photographs provided for each case. According to the diagnosis, a risk classification is added in the report, making the GP's decision for each specific case easier [31].

This structure is necessary and essential to providing standardization and reproducibility of these reports. In specific situations there is an open field so that the specialist can make comments relevant to the case or suggestions for diagnostic elucidation to the doctor. In short, it is a diagnostic test, in terms of a pathology, whereby the expert is responsible for the generated diagnosis and its consequences.

With the information for making the report inserted at the end, the report is published automatically and a protocol number is generated to access the doctor or the patient. This report can then be accessed through the portal and printed if necessary.

It is true that the correlation between the initial diagnosis and teledermatology diagnosis when obtained by dermatologists varies between 80.5% and 91.6% [4, 32]. However, with structuring of the acquisition of images through a fixed protocol, it is possible to increase the accuracy of a report by accessing appropriate specialists up to 40 times [6].

For example, with full service installation, during the first year 5,158 reports were issued. Of these 40.4% were suspected by the attending physician to be skin cancer in patients who would be scheduled for referral for consultation with the specialist. Through teledermatology, we were able to screen more than two-thirds of the patients who had benign lesions (seborrheic keratoses, nevi) without referrals [33] (Fig. 57.2).

Future Perspectives

This model, with the acquisition protocol photos and the structured reports, demonstrates the importance of using teledermatology as a modern health access tool. This diagnostic method enables the early detection of skin cancer and other skin diseases and reduces the number of unnecessary referrals to dermatologists, and therefore can reduce the waiting time for face-to-face consultations, as well as the costs associated with this process.

High rates of accuracy can be obtained with teledermatology both for adults and children, with affordable technical requirements. Furthermore, high rates of agreement are found for most common dermatologic lesion referrals.

Teledermatology can be used as a complementary tool in daily consultations at primary care centers and as an effective means to filter dermatology referrals. Nevertheless, integration with the health system (whether private or public) is essential to reduce the teleconsulta-
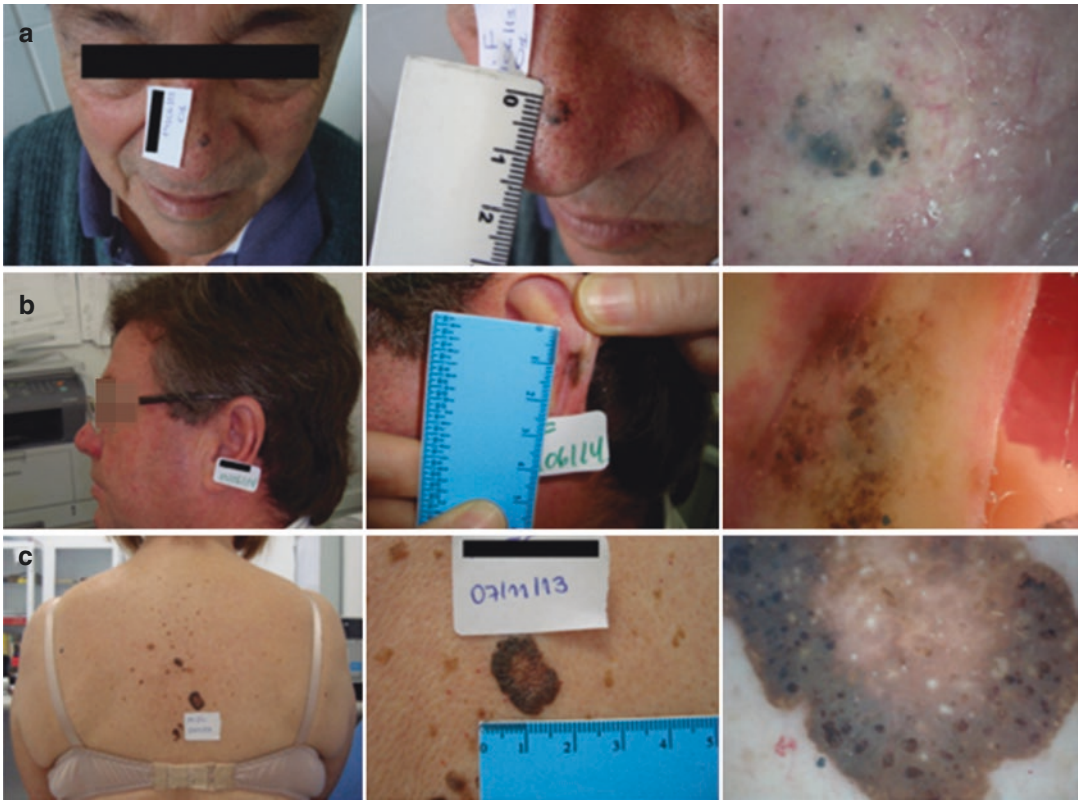
Fig. 57.2 Teledermatology cases. (**a**) Pigmented basal cell carcinoma. (**b**) Malignant melanoma. (**c**) Seborrheic keratosis

tion time, and training is needed to improve the quality of images [34].

Glossary

Second formative opinion Systematic response, based on literature review of the best scientific and clinical evidence and the directive role of primary health care. The questions originate from teleconsultation and are selected from criteria of relevance.

Tele-education Lectures, classes, and courses provided through the use of information and communication technologies.

Teleconsulting Registered consultation conducted among workers, professionals, and managers of health through bidirectional telecommunication instruments in order to answer questions about clinical procedures, health actions, and issues related to the work process. They can be of two types: (a) Synchronous – teleconsulting performed in real time, usually by chat, web, or video conferencing; or (b) asynchronous – teleconsulting performed by off-line messages.

Telediagnostics Autonomous service that uses information technology and communication to perform diagnostic support services through distance and time; e.g., Teleradiology, Teledermatology, Tele-electrocardiography.

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Signs and Symptoms of Skin Diseases in Public Health: A Practical Guide to Management

Stains

Roberta Castilhos da Silva, Mariele Bevilaqua, and Jenifer de Morais Silva

Key Points
- Stains configure an elementary dermatologic lesion of several common skin diseases in public health
- Pigmentary changes can be described as hyperchromic, hypochromic, and achromic stains
- Stains can be caused by vascular injuries or even be related to blood pigment
- This chapter provides an overview of the most prevalent skin diseases in public health that manifest as stains
- It is very important for the general physician to have a strategic flowchart to reach the etiologic diagnosis of each dermatosis that presents with stains

Introduction

The most important pigments that primarily determine the normal color of the skin are melanin, oxygenated reduced hemoglobin, and carotene [1].

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Other factors such as vascular supply, including number, caliber, and reactivity of blood vessels in the dermis, and epidermal thickness also influence the appearance of skin [2].

Melanocytes are located in the basal layer of the epidermis and contain specialized organelles that synthesize melanin released by dendrites as mature melanosomes. They arise from the neural crest during embryonic development. Three different types of melanin exist in human skin: eumelanin (brown or black), pheomelanin (red or yellow), and trichromes (present in various chemically well-defined variants). The gene for the melanocortin receptor 1 determines the level of melanin production. It is present in melanocytes and controls sensitivity to light exposure and sunburn, influences skin and hair color, and partly determines the individual risk of melanoma. The number and size of melanosomes cause variations in individual skin color and between persons of various ethnicities. Melanin synthesis is influenced by genetic factors and varies greatly among individuals, families, and ethnicities. Other factors include exposure to ultraviolet (UV) light, hormonal influences, and biochemical substances [3].

The term "stain" is used to describe an elementary dermatologic lesion that is flat and not palpable. It considers the term "spot" for a stain with a diameter less than 5 mm. The color of the lesion, which often is the first visual assessment, is an important additional feature and is repeatable in certain pathologies such as the destruction

of melanocytes, dilation of blood vessels in the dermis, or inflammation of the vascular wall with extravasation of red blood cells. Pigmentary changes can be described as hyperchromic, hypochromic, and depigmented or achromic [4].

Hyperpigmentation or hyperchromia results from increased melanin production caused by tyrosinase activity, increased melanocytes, and delayed breakdown and removal of melanin. On the other hand, hypopigmentation or hypochromia results from a reduction in the number of mature melanosomes and/or melanocytes or the abnormal transfer of mature melanosomes to neighboring keratinocytes [3].

From the point of view of semiology, we can divide the injuries of vascular stains into three main groups:

Transient or functional: always flat (stains), generally represented by erythema, which consists of reddish stain caused by cutaneous vasodilation; thus the digital pressure disappears

Cyanosis: characterized by a bluish spot on the skin due to lower local blood supply

Permanent: related to vascular proliferation (angiomas, hemangiomas), vascular dilatation (telangiectasia), and functional vascular constriction (nevus anemicus)

Furthermore, stains are also related to the blood pigment, when they are named purpura or hemorrhagic suffusion [5].

State of the Art and Future Perspectives

Skin disease is a common medical problem, becoming one of the most frequent reasons for consulting a general physician [6]. It represents 8.4% of primary care cases and can be a challenge to general physicians because of their general lack of knowledge and training in this area [7].

A study from the United Kingdom showed that, in primary care, the top three diagnoses were eczema (22.5%), infection and infestation (20.3%), and benign tumors (11.4%) [7], whereas

in secondary care the top three diagnoses were benign tumors (23.8%), malignant tumors (16.4%), and eczema (16.3%). The Brazilian Society of Dermatology conducted a study of the reasons for seeking a medical specialist in dermatology. Skin diseases with stains were common, with eczema, vitiligo, and leprosy being major reasons for visits [8].

As with other semiologic signs studied in dermatology, stains configure elementary lesions of several common skin diseases in public health. Recognizing and knowing how to characterize this sign makes performing a correct clinical diagnosis more simple and contributes to the solving capacity at the primary level of public health, whereby most of the problems presented by the population can be answered without the need to refer the patient to a specialist.

Hypochromic Stains

Leukoderma and hypopigmentation are general terms used to describe disorders characterized by whitening of the skin, which results from the decrease in epidermal melanin content (related to melanin) or cutaneous blood supply (related to hemoglobin).

Hypomelanosis is a specific term that expresses a level of deficiency or reduction of melanin, whereas melanosis is defined as total deficiency of skin color caused by lack of melanin pigments initially existent, as occurs in vitiligo. "Pigment breaking" is a term used to describe general reduction of skin color and hair color, as occurs in oculocutaneous albinism.

A summary of hypochromic stains is provided in Flowcharts 58.1 and 58.2.

Acquired Hypomelanosis

Vitiligo

Vitiligo is an acquired hypomelanosis of unknown etiology that is characterized by achromic stains, the result of a selective breakdown of functional epidermal melanocytes causing depigmentation
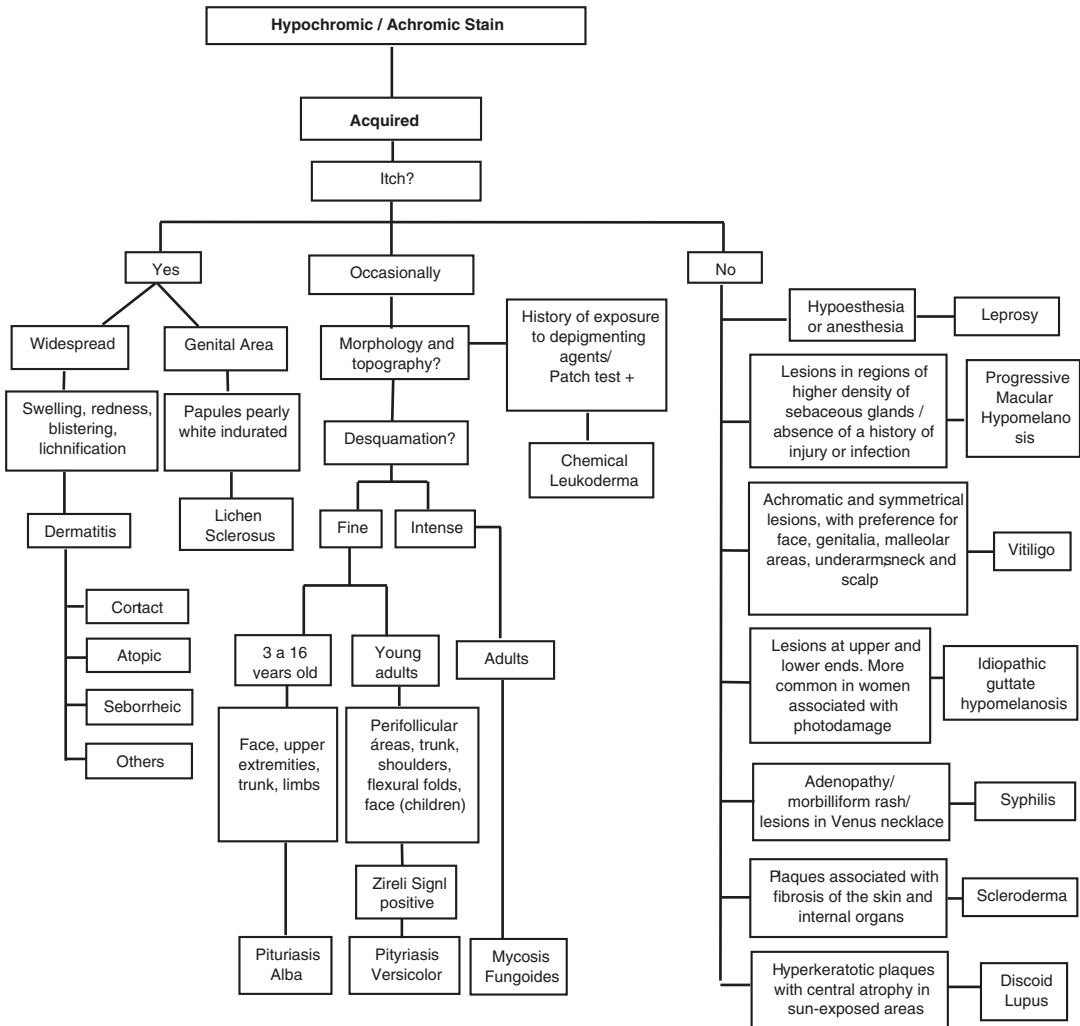
Flowchart 58.1 Acquired hypochromic and achromic stains

of the skin [8]. It is apparent in 0.1–2% of the world population, regardless of gender, age, or race [5]. Heredity is attributed to 30% of the cases [9–12]. Dermatologic lesions can also occur after trauma (Koebner's phenomenon), emotional stress, and sunburn [13, 14]. It is important to note that the evolution of the disease is unpredictable, and the lesions, likewise, can be extant or even slowly increase over the years.

Vitiligo clinically consists of the appearance of achromic stains that can initially be hypochromic, with clear limits and no associated symptoms; they generally have centrifugal growth [14]. The pattern shown by the disease is symmetric and predominantly focuses on malleolus, wrists, legs anterolaterally, back of hands, underarms, neck, scalp, and genitals (Fig. 58.1) [15]. Diagnosis is clinical and can be complemented using Wood's lamp or, rarely, a skin biopsy.

However, a fully effective treatment against vitiligo is not yet available. The main goal is the repigmentation of the skin and stability of the disease [15]. Among the factors to be considered in treatment strategies are the degree of the disease (stable or in progress), the psychological impact, and the age of the patient. Therefore, pho-

Flowchart 58.2
Congenital hypochromic
and achromic stains

```
┌─────────────────────────────────────────────┐
│        Hypochromic / Achromic Stain          │
└─────────────────────────────────────────────┘
                    │
        ┌───────────────────────┐
        │       Congenital       │
        └───────────────────────┘
```

Usually unilateral lesion with irregular borders and variable size	Nevus Achromicus
Pink-pale skin, white-yellow hair, visual changes	Albinism
Multiple lesions along the midline	Parcial Albinism
Lesion with triangular involving forehead and lock of hair + hyperchromic spots within the achromatic lesions	Piebaldism
Triad: mental retardation, epilepsy, facial angiofibromas	Tuberous Sclerosis
One or multiple lesions of polygonal shape or sheet format / irregular thckened plaques in the lumbosacral region	

Fig. 58.1 Vitiligo: achromic stains on the face (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

toprotection, topical and systemic corticosteroids, calcineurin inhibitors, analogs of vitamin D3, phototherapy, excimer laser, surgery, depigmentation, and covering are the therapeutic tools currently available [15, 16].

Guttate Leukoderma (Idiopathic Guttate Hypomelanosis)

Guttate leukoderma is an acquired and very common benign and asymptomatic dermatosis [17]. It is characterized by hypopigmented stains of about 0.5 mm diameter and has a smooth surface [18]. Guttate leukoderma affects mainly older people and women from all races [18, 19]. However, it is more common in dark skin pigmentation. It refers to a multifactorial disease that comprises repeated small traumas, genetic influence, and sun exposure as casual factors [20].

Lesion coverage includes mainly exposed areas of upper and lower extremities of the body, but other regions are, in the same way, commonly affected, except the facial area (Fig. 58.2) [21]. The lesions continuously change their dimensional aspect but increase in number. For this reason, aesthetic concerns become the main motivation for a dermatologic appointment.

The diagnosis is clinical [18]. A biopsy only is necessary when there is the need to differentiate from other diseases, such as vitiligo. Cryotherapy, superficial dermabrasion, topical retinoids, and topical tacrolimus 0.1% are some of the available therapeutic options [22, 23].
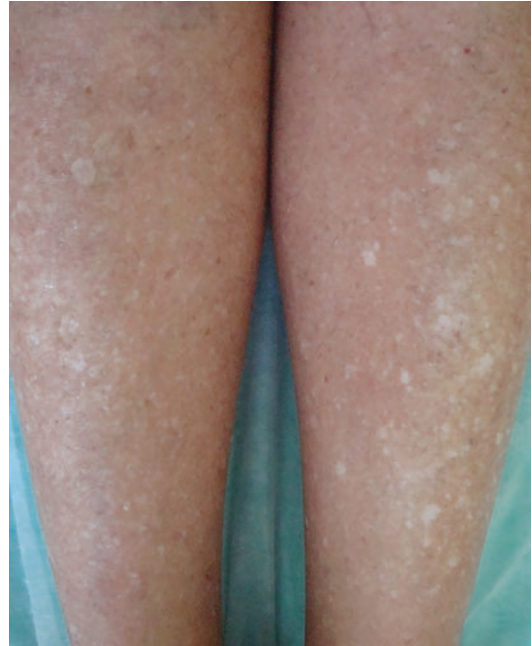
Fig. 58.2 Guttate leukoderma or idiopathic guttate hypomelanosis: hypopigmented stains on the lower limbs (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

Progressive Macular Hypomelanosis

Progressive macular hypomelanosis is a disease that affects mainly adults and young people [24]; the recommended pathogenesis consists in the use of *Propionibacterium acnes* as an element for the skin-lightening factor production that takes part in melanogenesis and causes hypopigmentation stains [5, 25, 26].

It is clinically defined as multiple nummular and confluent hypochromic macules, symmetric and asymptomatic [27]. The lesions mainly appear in areas of higher density of sebaceous glands, as in the midsection and they tend to converge in the midline, although they also can move to the neck and the upper extremities [28, 29] (Fig. 58.3). Progressive macular hypomelanosis has clearly been shown to be a persistent disease that develops over several years and then becomes stabilizing; in some cases it can regress.

The diagnosis is clinical and is completed by use of the Wood's lamp method, which shows red follicular fluorescence restricted to the injured area [30].

The treatment is off-label. However, the likely implication of *P. acnes* in the pathogenesis has prompted the use of drugs with activity against the bacteria. The use of topical benzoyl peroxide 5%, or clindamycin 1%, or systemic use of lymecycline 300 mg/day or minocycline 100 mg, for 3 months, are some of the recommended drugs [5, 31]. Phototherapy has been proved to be effective, but it does not prevent recurrence of the disease [32]. In some patients, there is transient pigmentation after sun exposure.

Postinflammatory Hypomelanosis

Pityriasis Alba
Pityriasis alba is a benign dermatosis that affects mainly children between the ages of 3 and 16 years old. Although no definitive cause has yet been found, it has been associated with atopy and sun exposure [33–35].

The disease affects the patient's face and upper extremities and, occasionally, the midsection and the lower extremities. Its development follows three steps: erythematous plaques that can cause itching come first; after a few weeks, the rash disappears and fine scale stains appear; in the final stage of disease development, hypopigmentation macules [34, 36] round or oval from 0.5 to 5 cm diameter, with defined edges, and usually asymptomatic, are observed [36, 37]. These hypopigmentation macules can remain for years or regress in some months.

The main differential diagnosis is pityriasis versicolor, and mycologic examination is often essential in order to confirm the differential [38]. For treatment, low-dose topical glucocorticoids, calcineurin inhibitors, and emollients are preferable to moisturize the skin and speed up the pigmentation [35].

Hypopigmented Mycosis Fungoides
Hypopigmented mycosis fungoides is a variation of the first phase of mycosis fungoides, and is much more common in individuals with intensive
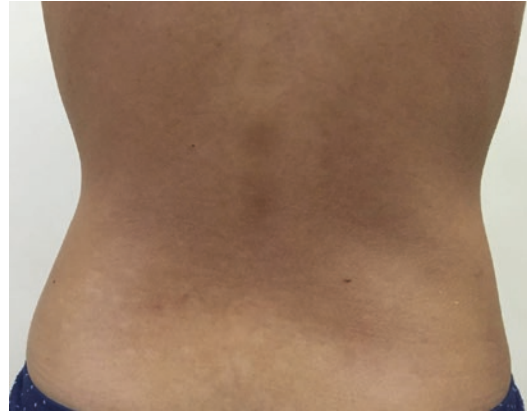
Fig. 58.3 Progressive macular hypomelanosis: confluent hypopigmented macules involving the torso (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

Fig. 58.4 Hypopigmented mycosis fungoides: hypopigmented lesions in the proximal lower limbs (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

sun exposure and evidence of lesions. The hypopigmented lesions occur in the midsection or the extremities of the body (Fig. 58.4), possibly accompanied by uncomfortable itching and erythema. The appropriate treatment consists in the use of nitrogen gas or phototherapy [18].

Scleroderma
Scleroderma is a connective tissue disease of unknown origin and slow evolution that leads to fibrosis of skin, blood vessels, and internal organs

[39]. The disease presents two types: restricted scleroderma (morphea) and systemic [40]. The morphea also presents in other forms: cutaneous hypochromic stain (Fig. 58.5), consisting of a clear erythematous plaque of ivory and yellow center, smooth and shiny blue and violet shades; hypochromic atrophic plaque, with central depression, papule, or skin-colored plaque that resembles keloids; and injury to the frontal or frontoparietal region that causes grooves [40, 41]. It can be progressive and can affect the entire hemiface (morphea "en coup de sabre"). The systemic scleroderma can develop either in a hyperchromic or hypochromic way [42]. It is characterized by retaining segments at the level of the hair follicles, causing an appearance that resembles salt and pepper. Systemic scleroderma appears commonly in the upper midsection and on the patient's face [43]. The options for treatment are scarce; in general, therapy attempts to control the characteristics of the affected organ [43, 44].

Lichen Sclerosus

Lichen sclerosus is a disease of unknown origin, but is multifactorial disease [45]. Although lichen sclerosus seems to be a skin disorder, it predominantly affects the external genitalia and anal region; in males, the disease affects most frequently the area of the glans [45–47]. Genital and extragenital lesions of lichen sclerosus are often hypopigmented (Fig. 58.6). Other characteristics of the disease are pearly white, polygonal, and flattened papules, atrophy, and corneal pimples [46, 48]. The main purpose of treatment is to gain control over the symptoms, and to detect and treat early overlying neoplasms [9].

Discoid Lupus

Lupus is an autoimmune and multisystemic disease whose appearance is much more common in women; it clinically appears in all skin areas [49]. Lupus can have only a cutaneous appearance and can be associated with systemic disorders, although it is rarely a systemic injury.

The appearance of chronic cutaneous lupus, such as discoid injury, is less likely to develop into systemic involvement [50]. The injuries are initially apparent as well-limited erythematous hyperkeratotic plaques, with adherent scaling and

Fig. 58.5 Scleroderma: hypochromic and atrophic stain (morphea) on the neck (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)
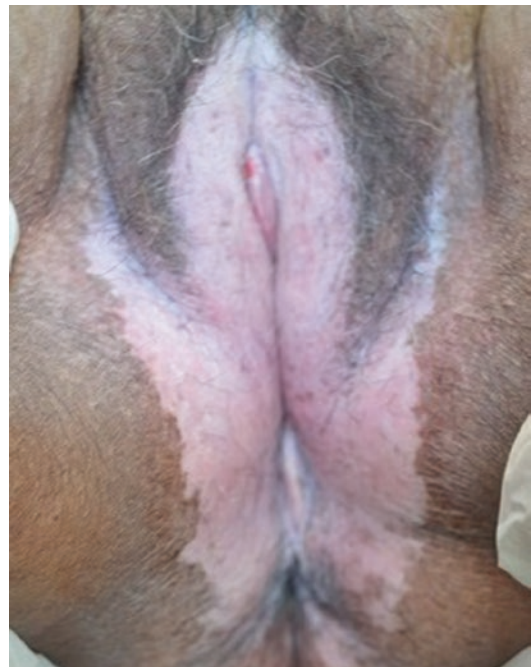
Fig. 58.6 Lichen sclerosus: hypopigmented stain in the genital area (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

Fig. 58.7 Discoid lupus: erythematous lesions with achromic (vitiligoid) and hypochromic areas associated with atrophy (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

Table 58.1 Vitiligo × chemical leukoderma

1. Acquired vitiligo-like depigmented lesion(s)
2. History of repeated exposure to specific chemical compounds
3. Patterned vitiligo-like macules conforming to site of exposure
4. Confetti macules

gradual development to central atrophy [49]. The achromia, which refers to a vitiligoid or hypochromic feature on the lesion, is frequently associated with skin atrophy (Fig. 58.7) [51]. The most affected areas are those exposed to sunlight.

The diagnosis is reached by clinical examination and confirmed by histopathologic examination [52]. Glucocorticoid and calcineurin inhibitors are used for topical treatment. For systemic treatment, antimalarials, retinoids, and thalidomide are suggested drugs, according to the degree of injury [49, 53].

Leukoderma by Chemical Substance

Chemical leukoderma is an acquired dermatosis caused by repeated exposure to certain chemical or pharmacologic compounds, which carry consequences of burning, destruction of melanocytes, and achromatic scars. The main depigmentation groups are phenols/catechol, sulfhydryl, and miscellaneous, harmful only to genetically susceptible persons [5, 18]. The effect caused by the use of these compounds can be: (a) selective destruction of melanocytes; (b) inhibiting the function or structure of the melanosome; (c) inhibition of tyrosinase biosynthesis; (d) inhibiting the nature of melanin; (e) involvement in the transfer from melanosomes to keratinocytes; (f) the effect of chemicals compound on melanin or damage to melanin [54].

For treatment, the most widely recommended phenolic compound is monobenzyl ether of hydroquinone, often used in the rubber industry (gloves, shoes, glasses, condoms, etc.) [5]. This compound can cause achromatic stains with morphotopography of the object it contacts. For cosmetic treatment against the melasma, the depigmentation caused by use of the compound is supposed to be definitive, and appears as a confetti pattern [54, 55]. Other phenol compounds and catechols (bultifenol and aminophenol) exist in germicides, insecticides, resins, deodorants, and detergents, and can cause hypochromia or achromia of the skin, even in areas where close contact, by inhalation, does not occur [5, 12].

However, it is noteworthy that clinical differentiation between chemical leukoderma and vitiligo is not easy [56] (Table 58.1).

In some cases, chemical leukoderma can also cause pruritus. Patch tests are a useful tool for this diagnosis. Repeated examinations are important for it to be effective (e.g., in 2 weeks, repeated at 4 weeks and 6 weeks) [18]. Biopsy is only necessary in controversial cases [57]. In some situations, after removal of the causative agent, monitoring of the skin pigmentation is advisable.

Infectious/Parasitic Hypomelanosis

Pityriasis Versicolor

Pityriasis versicolor is a chronic fungal infection of the skin caused by *Malassezia furfur* [58]. These fungi normally settle in sebum areas (scalp, face, back, midsection) and clinical development occurs in certain circumstances whereby the equilibrium of the skin changes, such as age, sex, race, genetic capacity, high level of hydration, and oily substances in skin, allowing the pseudofilaments of yeast to grow [9, 58]. Pityriasis versicolor can appear as outbreaks or becomes recurrent or chronic.

The diagnosis is clinical and easily noticed by multiple round or oval stains or thin plaques

with desquamation (noticeable by Zireli's sign) which shows glossy or matt smooth surface, usually asymptomatic (Fig. 58.8) [59]. The stains can vary in color from white to brown and, more rarely, erythema [9, 60]. For this reason the name, versicolor, is one of the disease features. The hypopigmentation lesions occur by the action of inhibitory effects on the melanocytes, through the production of dicarboxylic acids by the yeast [61]. Initially, the filaments present a perifollicular feature, but after time grow and merge to form irregular stains of larger extent.

The final diagnosis is by direct mycologic examination and Wood's lamp, which confirm a yellow or silver fluorescent characteristic in the stains [62].

Treatment comprises the use of topical agents alone or in combination with systemic therapy [9, 62]. The prophylaxis is acceptable for recurrent cases. The hypopigmentation may persist for several months even after conclusion of the treatment.

Leprosy

Leprosy is a chronic, contagious, and infectious disease of potentially disabling outcome, caused by *Mycobacterium leprae*, which mainly affects the skin and the peripheral nerves [5, 63]. The patient who carries the infected bacillus is the main source of infection, and transmission occurs through the upper airway or by direct contact with the injury [5, 63–65]. Leprosy can be divided into two groups: tuberculoid (paucibacillary) and virchowian (multibacillary); and into two unstable types: indeterminate (which can develop into any form of leprosy) and dimorphic or borderline [12]. The World Health Organization has proposed a simple classification for operational purposes: paucibacillary (indeterminate and tuberculoid) and multibacillary (virchowian and borderline) [9].

Paucibacillary forms of the disease present with hypochromic stains, and for this reason they are included in the differential diagnosis for other dermatoses showing similarly appearing lesions. Indeterminate leprosy is the first manifestation of the disease and presents as hypochromic macules or slight erythema with hypoesthesia (Fig. 58.9) [66, 67]. There are usually few injuries with no specific area of affection, and the edges of lesions can be a clear or strongly outlined. Generally in the injured area there is some nerve fiber loss. In this case, the largest diameter of nerves is not impaired and, therefore, there is no resulting disability [9].

Fig. 58.8 Pityriasis versicolor: multiple round and oval stains with desquamation on the trunk (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

Fig. 58.9 Indeterminate leprosy: hypochromic stain with hypoesthesia on the back (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

In other cases, different from paucibacillary forms in tuberculoid leprosy, lesions are macules and erythematous plaques of varying sizes, with strong outline and regular papular rash [67]. They appear in classical form, being circular and asymmetric lesions, usually single or in a cluster. The sensorial disturbances are severe, and important asymmetric and neural involvement, with thickening of peripheral nerves, can occur; the reduction or absence of nerve fibers in the affected area can occur [5, 67].

The diagnosis is clinical and the treatment has been effective. The first-line drugs are dapsone, rifampicin, and clofazimine [65, 66]. The differential diagnosis of paucibacillary leprosy includes achromic nevi, pityriasis alba, tinea versicolor, discoid lupus erythematosus, secondary and tertiary syphilis, circular granuloma, multiform granuloma, lichen planus, leishmaniasis, sarcoidosis, and vitiligo, among other diseases [63, 68, 69]. As a rule, no hypochromic lesion with preserved thermal and pain sensitivity is leprosy.

Syphilis

Syphilis is a contagious and infectious disease caused by the bacterium *Treponema pallidum* and is mainly transmitted through sexual intercourse [70, 71]. It follows a systematic pattern and if left untreated, and progresses to chronically alternating periods of activity and remission. Acquired syphilis comprises two types: recent (1 year or less of evolution; it encompasses the primary form, secondary and latent) and late (more than 1 year of evolution; it encompasses the tertiary form) [9].

In secondary syphilis the rash appears in different forms and structures and frequently similar to injuries of other diseases; for this reason secondary syphilis is named "the great imitator," a factor that has always been included in differential diagnosis of hypochromic macules [5].

In secondary disease a nonpruritic morbilliform rash comes first, exhibiting round or oval erythematous macules and papules, named syphilitic rose stains [70, 72]. These progress symmetrically through the midsection and continue throughout the body, including the palm and the sole regions [73]. Peripheral desquamation, in some lesions, is known as Biett's collarette. Residual hypochromic lesions form a lens shape around the neck, known as "necklace of Venus," and can be present after secondary degree syphilis [12].

The diagnosis of syphilis is by direct search of *T. pallidum* in a dark-field and serum area examination. The treatment comprises penicillin G benzathine in varying dosages according to the degree of the disease [74].

Hereditary and Congenital Hypomelanosis

Albinism

Albinism is a group of genetic diseases, of autosomal recessive pattern, characterized by a defect in melanin synthesis, but with the structure and complement of ordinary melanocytes [5]. The oculocutaneous albinism segment, which comprises four different diseases, constitutes hypopigmentation of the skin, hair, and eyes. It becomes ocular albinism when it focuses on the retinal epithelium [5, 18]. Skin involvement can occur by itself, but this is less common.

Albinism can be categorized in two branches: complete (universal) or incomplete (partial) [75]. Incomplete albinism is a variant of the disease whereby the skin tends to have slight pigmentation, the hairs are clear, and the ophthalmologic changes are less frequent. It is identified by hypopigmented lesions that are usually multiple and been present along the midline of the body since the patient's birth [18]. The main difference, related to the diagnosis, in this case, is the vitiligo.

The primary treatment against the disease is strong photoprotection of the skin and the eyes, beginning at the patient's birth, as well as no exposure to UV radiation [5, 18, 75]. Cryosurgery, curettage, electrocoagulation, and early ablation of keratosis and malignant neoplasms are normally the methods used as therapy in cases of photoinjuries to the skin [75].

Fig. 58.10 Piebaldism: symmetric achromic stains on the abdomen and extremities (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

Piebaldism

Piebaldism is a rare congenital autosomal dominant leukoderma, caused by a mutation in the involved gene, in the development of melanoblast (C-KIT gene) [5].

Clinically the disease initially presents at the patient's birth, and consists of achromic and triangular-shaped stains specifically placed on the forehead with a lock of hair (poliosis) next to it, including the eyelashes; the skin discolorations, strictly symmetric, can also affect the chest, abdomen, and extremities, although the back is spared (Fig. 58.10) [5, 12].

The leukoderma is, generally, a stable disease that follows the growth of the patient. An interesting characteristic of this disease is the presence of pigmented stains or hyperchromic macules in the achromic injury, which aids the differential diagnosis of vitiligo [5]. Photoprotection is essential, and the recommended treatment involves transplantation of melanocytes, assuming the lesions do not respond to topical treatment and phototherapy [12, 76].

Tuberous Sclerosis

Tuberous sclerosis is a complex, autosomal dominant neurocutaneous syndrome characterized by hamartomas in many organs, especially the skin.

Fig. 58.11 Tuberous sclerosis: macule in leaf shape located on the leg (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

The classic triad consists of mental retardation, epilepsy, and facial angiofibromas [77].

Cutaneous lesions of many types occur. The hypochromic macules (usually present at birth) vary in number from one to tens and are mostly small, polygonal, or in a fingerprint shape [78]. Another version of the hypochromic lesion is mac-

ules in leaf shape (Fig. 58.11), which is less common but characteristic. Also part of the syndrome's cutaneous manifestations are thick irregular plaques that occur in the midsection, commonly in the lumbosacral region (Shagreen patches) [79].

The treatment is complex. For skin lesions, electrosurgery, dermabrasion, and laser therapy are more common [78, 80].

Nevus Achromicus

Nevus achromicus (also known as nevus depigmentosus) is a achromic congenital stain with irregular border and variable size and stability [81, 82] (Fig. 58.12). It manifests segmentally or, less commonly, is widespread. Usually it is a single lesion diagnosed at birth or in childhood. In most patients, it appears in midsection or proximal portion ends and does not cross the midline [81]. It can affect both men and women

Fig. 58.12 Nevus achromicus: achromic stain with irregular border on the neck (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

Table 58.2 Diagnostic criteria for nevus achromicus

1. Leukoderma presents at birth or early childhood
2. Leukorderma distribution unchanged for the entire life
3. No texture or sense change in the affected area
4. Absence of hyperpigmentation border around the achromic area

equally, and its physiopathology is likely associated with a defective development of fetal melanocytes. The diagnosis is clinical [83] (Table 58.2). The biopsy typically displays a hypomelanotic, but not melanocytic, lesion, rendering the term "nevus achromicus" inappropriate [84].

The main differential diagnoses are vitiligo and nevus anemicus for strict shape and Ito hypomelanosis for target and systematic shapes. The Wood's lamp examination indicates hypochromia, but without the whitish-pink color from vitiligo [81]. The appearance and frequency of the lesions are also important criteria in determining vitiligo. The treatment available for repigmentation are phototherapy, excimer laser and surgical grafting [85, 86]. However, the results of these therapies are inconsistent and recurrence is possible.

Hyperchromic Stains

Hyperpigmentation is due to an increased melanin production caused by increased melanocyte and tyrosinase activity, as well as delayed breakdown and removal of melanin [18]. Hyperchromic stain appears as brown shades over the skin. It can be single, isolated, or multiple and widespread, in many geometric patterns. Many hyperpigmentation disorders are acquired or idiopathic, although some may be influenced by genetic, systemic, or environmental factors [18].

A summary of hyperchromic stains is provided in Flowchart 58.3.

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                          ┌─────────────────────────────┐
                          │      HYPERCHROMIC STAINS     │
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HYPERCHROMIC STAINS

ACQUIRED HYPERCHROMIA

Postinflammatory
Melasma
Phytophotodermatitis
Erythema Dyschromicum Perstans
Fixed Drug Eruption
Flagellate Dermatitis
Poikiloderma of Civatte
Lichen Planus Pigmentosus

SECONDARY TO COMPONENTS EXTERNAL

Ocronosis
Drugas (table 69.4)
Chemical agents (Table 69.5)

SECUNDARY TO SYSTEMIC DISEASES

Addison desease
Cutaneous Amiloidosis
Mastocitosis

HEREDITARY HYPERCHROMIA

Mongolian Spot
Nevus of Ota
Nevus of Ito
Becker nevus
Speckled lentiginous Nevus
Ephelides (Freckles)
Café au lait spots

GENETIC DISEASES (Table 69.3)

Laugier-Hunziker Syndrome
Mc Cune Albright Syndrome
Reticulate Acropigmentation of Kitamura
Franceschetti -Naegeli Jadassohn Syndrome
Cronkhite-Canada Syndrome
Fanconi Syndrome

Dyschromatosis

Peutz Jeghers Syndrome

MELANOCYTIC LESIONS

Melanoma
Melanocytic Nevus: congenital or acquired
Lentigines
Melanin Stains: of lips, penile, and vulva

Flowchart 58.3 Hyperchromic stains

Acquired Hyperchromic Stains

Postinflammatory Hyperpigmentation

Postinflammatory hyperpigmentation represents an excess of melanin acquired after inflammation or skin lesion. It is extremely common and it can occur on any part of the skin surface, including mucous membrane and nails. It affects individuals of any age, regardless of gender preference. People with high phototypes tend to be affected more frequently and severely. Lesions can become worse after uninterrupted inflammation, trauma, or sun exposure [18].

The stains are asymptomatic, their color varying from brass color to dark brown or from bluish gray to greyish brown. The primary lesions of underlying inflammatory disorder may or may not be evident when mixed with hyperpigmentation. When there is no primary lesion the size, shape, and pattern of hyperpigmentation lesion distribution suggest the underlying etiology (Fig. 58.13) [18].

Disorders that cause postinflammatory hyperpigmentation include acne, insect bites, pyoderma, atopic dermatitis, psoriasis, pityriasis rosea, lichenoid drug reactions, systemic lupus erythematosus, and fixed drug eruptions.

Treatment focuses on treating the underlying cause, even with lesion regression that ceases over time; treatment can take months or years in patients with darker skin [18].

Melasma

Melasma is an acquired disorder characterized by symmetric and hyperpigmented stains of irregular shape that occurs more often on the face. It is most prevalent in young and middle-aged women. Exacerbating factors include pregnancy, use of oral contraceptives, sun exposure and, rarely, use of phenytoin on human immunodeficiency virus (HIV) patients. Although the exact pathogenesis of melasma is unknown, there is no evidence that after sun exposure (or another inductor) the hyperfunctional melanocytes in exposed skin cause an increased production of melanin [18].

The most common clinical pattern according to region of the lesion is the centrofacial (malar region, supralabial, nose, and mentum). Other patterns are malar (cheeks and nose) and mandibular (mandible branches) (Fig. 58.14).

The disease can be epidermal (resulting from increase of melanin in the basal and suprabasal layer of epidermis) or dermal (melanin in perivascular macrophage clusters). The diagnosis is essentially clinical, and a combination of hydroquinone (2–4%), tretinoin (0.05–0.1%), and a corticosteroid is the most common treatment [87].

Phytophotodermatitis

Phytophotodermatitis is a common disease characterized by a rash that occurs after contact with photosensitizing compounds in plants and sun exposure. It does not need previous exposure to furocoumarins. The acute form of the disease may be asymptomatic or can cause itching and burning, with erythema and vesiculation depending on the amount of skin contact, the skin color, and intensity of sun exposure. After resolution of the inflammation, the affected area has marked hyperpigmentation (Fig. 58.15). Many plants have been identified that contain furocoumarins,

Fig. 58.15 Phytophotodermatitis: hyperpigmentation on the hand due to contact with plant and subsequent sun exposure (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

including limes, lemons, and celery. The extract of this plant makes use in chemical components of some perfumes and colognes, inducing "Berloque dermatitis" or "au-de-cologne dermatitis" [88].

The diagnosis is clinical, and treatment for acute inflammatory lesions includes the use of a topical steroid and cold compress. After the reduction of inflammation, it is advisable to discontinue the topical steroids. To prevent more hyperpigmentation, the use of sunscreen is fundamental. The hyperpigmentation areas usually fade with time, but a bleaching agent is an option if skin discoloration persists [89].

Erythema Dyschromicum Perstans

Erythema dyschromicum perstans is an uncommon disease of unknown etiology and it well known for its chronic appearance, also known as "gray dermatosis." It is more common in people with high phototypes and can be associated with endocrinopathies, ingestion of ammonia nitrate, radiologic contrast, vitiligo, HIV, and chronic hepatitis C infection. Most of the cases do not have an identifiable triggering factor. Some studies point to an immune-mediated dermatosis, likely with a genetic predisposition, as initiating the disease. The lesions described are asymptomatic and symmetric stains colored

gray-brown, located on the midsection, face, and extremities, except the palms, sole, scalp, and hands.

Diagnosis focuses on clinical presentation and histopathologic findings. Differential diagnosis includes lichen planus pigmentosus, idiopathic eruptive macular pigmentation, postinflammatory hyperpigmentation, fixed pigmented erythema, Addison's disease, and hemochromatosis. Treatment is based on the topical use of hydroquinone, topical corticosteroids, and tretinoin, although the results may be not so good because of the dermal deposits of melanin. Clofazimine and dapsone can be used in adult patients because of their anti-inflammatory and immunomodulatory activity [87].

Fixed Pigmented Erythema

Fixed pigmented erythema is a type of pharmacodermia characterized by lesions that occur for 1–2 weeks after the first exposure to certain medicines, with resurgence within 24 h in the same place via a new exposure.

Clinically it is visible as erythematous and edematous rounded stains or plaques, sharply demarcated, and sometimes with gray and violet hue (Figs. 58.16 and 58.17), in addition to the central blister. It can be found anywhere on the body but prevails in the lips, face, hands, feet, and genitalia. The lesions gradually disappear in several days, leaving a postinflammatory

Fig. 58.16 Fixed pigmented erythema: erythematous and edematous rounded stain on the wrist (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

Fig. 58.17 Fixed pigmented erythema: multiple stains with *violet* hue on the trunk (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

Fig. 58.18 Flagellate dermatitis: erythematous and hyperchromic linear stains on the upper limbs (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

hyperpigmentation residue. The most common medications used for treatment are sulfonamides, anti-inflammatories, barbiturates, tetracycline, acetaminophen, and tetryzoline. It is a clinical and sometimes histopathologic diagnosis. The treatment consists of removing the triggering agent [18].

Flagellate Dermatitis

Flagellate dermatitis, or flagellate erythema, is a cutaneous toxic effect unleashed by bleomycin, with a rate of incidence of 8–20% regardless of the path of administration or the types of malignant disease to be treated. The reaction usually occurs after accumulative doses of 100–300 mg. The time between drug administration and the appearance of lesions varies and can last up to 6 months. Clinically it presents as linear stains with adjacent pruritic erythematous papules that may show occasional bleeding or pustules. It appears on the upper chest and back, but also on the limbs and flanks (Fig. 58.18) [87].

As the rashes become less erythematous, the affected areas become hyperpigmented. Most cases can be reverted after discontinuation of the offending agent. Antihistamines and the use of topical and oral corticosteroids can reduce pruritus [18].

Poikiloderma de Riehl-Civatte

Poikiloderma of Civatte is an acquired and commonly benign dermatosis that affects fair-skinned, middle-aged, and elderly people. The etiology is multifactorial and includes chronic sun exposure, menopause-related hormonal changes, contact hypersensitivity, and genetic predisposition. Clinically it consists of telangiectasia, cutaneous atrophy, and macular hypo- and hyperpigmentation that appears symmetrically on the sides, as a V-shaped area on the neck, and on the lateral parts of the face with sparing of anatomically shaded areas (Fig. 58.19) [90, 91].

Because of the variations in clinical appearance, a classification proposes to categorize the disease into erythematotelangiectatic type, pigmented type, and mixed type, which also assists in determining the most appropriate treatment [92]. Treatment consists mainly of educating patients to avoid sun exposure and regular use of sunscreen. Laser treatment can be used, but with varying results.

Lichen Planus Pigmentosus

Lichen planus pigmentosus is an uncommon variation of lichen planus that affects mostly middle-aged adults with high cutaneous phototypes. Its etiology is still unknown, but sun exposure may be involved because of the

Fig. 58.19 Poikiloderma of Civatte: symmetric telangiectasias and hyperpigmentation on the V-shaped area on the neck (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

Fig. 58.20 Mongolian spot: stain with *blue-black* pigmentation located on the gluteal area (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

photodistribution. It appears as stains and plaques with irregular oval shape, usually symmetric and with coloration ranging from brown to grayish-brown in sun-exposed or scarred areas. The early lesions differ from erythema dyschromicum perstans by not presenting an erythematous border. It is usually asymptomatic, although some patients describe a light itch or burning sensation. The clinical diagnosis is obtained by histopathology; as yet there is no effective treatment [18].

Hereditary Hyperchromic Stains

Mongolian Spot

Mongolian spot is a congenital stain with blue-black pigmentation, unique or multiple, located on lumbosacral and gluteal areas and lower portion of the scapula with varying size and shape (Fig. 58.20). It is frequent in yellow and black races. It is present at birth and tends to disappear between 3 and 5 years old, but can remain during childhood or adulthood. The diagnosis is clinical and there is no need for treatment, since it usually regresses spontaneously and presents benign features [18].

Nevus of Ota

Nevus of Ota derives from melanocytes located on the innervation of the ophthalmic and maxillary branches of the nerve trigeminal areas. It appears at birth or in adolescence, mostly in women. Clinically it is an irregular stain, edge set, and grayish blue in color, unilaterally located in the periorbital, malar, or nasal region (Fig. 58.21). It usually affects the sclera of the ipsilateral eye. As it can be associated with increased intraocular pressure, it is important to request an ophthalmologic examination and careful follow-up [18].

Nevus of Ito

This nevus presents the same characteristics as nevus of Ota, but differs in location. It occurs in innervated areas of the tracheocutaneous lateral and anterior supratrochlear nerves (shoulders, supraclavicular, and neck regions). The indicated therapy is similar to that for nevus of Ota [18].

Becker Nevus
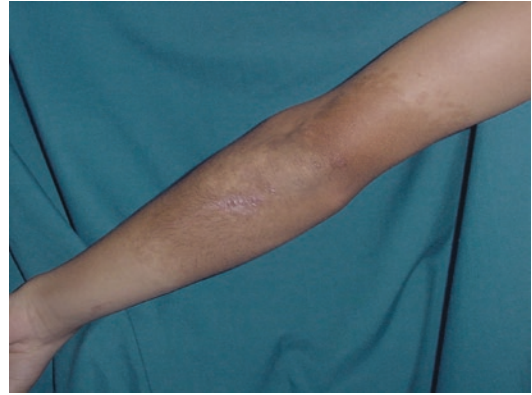
Becker nevus is a hamartoma that affects mostly young men. It appears as an irregular pigmented stain located on the shoulder, upper chest, or scapular region (Fig. 58.22). During puberty, dark and thick hair appears in the lesion, and does not always affect the pigmentation area [18].

Speckled Lentiginous Nevus
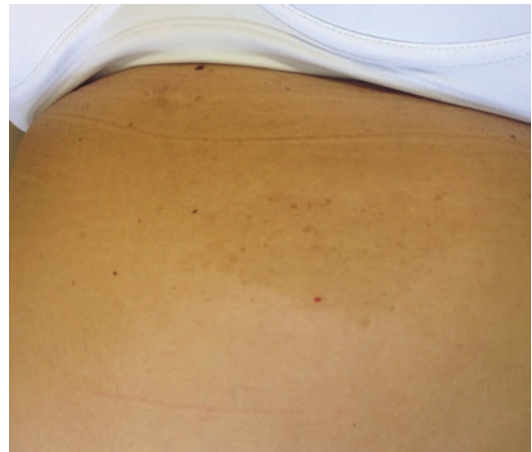
Speckled lentiginous nevus appears as an irregular brownish stain (similar to coffee with milk) with darker pigmentary punctate lesions and histological features of simple lentiginous or compound nerves (Fig. 58.23). It begins usually at pre-school age, and the data regarding malignant potential are insufficient [18].

Ephelides (Freckles)

Freckles are caused by an increase of melanin pigment in the melanocytes. They are macules of brownish color that are prevalent in sun-exposed areas of the skin. Freckles occur on the nose and malar area, forehead, and dorsum of the hands, as a sign of photoaging, but may also appear in younger age groups, especially in those with fair skin. The diagnosis is clinical and the treatment is purely for cosmetic reasons, including the use of chemicals such as α-hydroxy acids, trichloroacetic acid, phenol, and Jessner's solution. Electrosurgery, cryotherapy, and lasers are also treatment options. These treatments have not proved to be completely satisfactory and have a common risk of postinflammatory hyperpigmentation [93, 94].

Café-au-Lait Spots

Café-au-lait spots may be present at birth or develop during the first years of life. They have a uniform pigmentation and a sharp border, and range in size from 0.2 to 30 cm in diameter. They are also indicators for various genodermatoses, especially neurofibromatosis. More than five café-au-lait lesions are suggestive of neurofibromatosis. Examinations of axillary freckling (Crowe sign) and iris hamartomas (Lisch nodules) are advisable. Other rare genetic syndromes such as Albright syndrome and Cowden syndrome are also associated with café-au-lait stains [3].

Other Genetic Hyperpigmentations

Other genetic diseases that can cause hyperpigmentation are listed in Table 58.3.

Hyperchromia Secondary to Systemic Diseases

Addison Disease

Addison's disease is a primary adrenal insufficiency that results in glucocorticoid and mineralocorticoid deficiency. Acute adrenal crisis results from orthostatic hypotension, fever, and hypoglycemia. Chronic primary adrenal insufficiency is characterized by a more frequent history of malaria, anorexia, diarrhea, weight loss, and joint and back pain [95].

The cutaneous manifestations include darkening of the skin, especially in sun-exposed areas, and hyperpigmentation of the palmar creases, frictional surfaces, vermilion border, recent scars, genital skin, and oral mucosa. Measurement of basal plasma cortisol is an

Table 58.3 Other genetic diseases associated with hyperpigmentation

Peutz–Jeghers syndrome
Laugier–Hunziker syndrome
McCune–Albright syndrome
Reticulate acropigmentation of Kitamura
Franceschetti–Naegeli–Jadassohn syndrome
Cronkhite-Canada syndrome
Fanconi syndrome
Dyschromatosis
Incontinentia pigmenti

insensitive screening test. Synthetic adrenocorticotropin 1–24 at a dose of 250 µg is an effective dynamic test. Elevated plasma levels of adrenocorticotropin and renin confirm the diagnosis. Treatment involves hormonal replacement therapy [96].

Cutaneous Amyloidosis

Cutaneous amyloidosis is a deposit of amyloid substance in the skin and internal organs. It can be classified in primary and secondary, systemic or localized, and hereditary or acquired. The primary and secondary forms can be systemic or localized. The form most associated with neoplasms is the primary systemic, which appears at a rate of 10–20% in individuals with multiple myeloma. The dermatologic clinical condition usually adopts a general systemic appearance and begins with hemorrhagic lesions caused by a deposit of amyloid in the vessels walls, causing vascular fragility. Features around the eyes may appear as ecchymotic lesions, known as raccoon sign. Alopecia and cutis verticis gyrata in the scalp could appear. Linear hemorrhagic lesions in the midsection (Koebner's phenomenon) may be present. Macroglossia presents in 40% of cases. The clinical diagnosis by histopathology is definitive. Systemic change occurs throughout the affected organ. There is no effective treatment. Some studies showed good response to melphalan in conjunction with prednisone. The progression of the disease most commonly leads to death within 2 years [18].

Mastocytosis

Cutaneous mastocytosis is a spectrum of disorders characterized by accumulation of normal mast cells in the skin and sometimes other organs. Systemic signs and symptoms include flushing, blistering, pruritus, and diarrhea, due to histamine degranulation and by release of physical and dermatologic impulse. Systemic disease may involve the gastrointestinal tract, the bone marrow, or other organs. In children, the disease is typically limited to the skin; however, painless systemic mastocytosis is also common. The classic form related to hyperpigmentation is urticaria pigmentosa, when patients develop stains and brown to reddish-brown papules, presenting as a

Fig. 58.24 Urticarial pigmentosa: stains and *brown* to *reddish-brown* papules, as a prickly rash mostly in midsection spreading symmetrically (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

Fig. 58.25 Darier's sign: the cutaneous mastocytosis lesions usually become irritated after suffering friction (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

Hyperchromia Secondary to External Components

The affinity of melanin biopolymers for metal ions, drugs, and other organic compounds is an important factor in the etiology of some hyperpigmentation disorders [98].

Ocronosis

Exogenous ochronosis is an unintended side effect for patients who already being treated with hydroquinone for long-term hyperpigmentation disorders in sun-exposed areas. Early diagnosis is the key in ensuring that the offending agent is suspended. The diagnosis is clinical, the presence of dark stains in areas previously treated with hydroquinone being important (Fig. 58.26). Dermatoscopy can be useful and may negate the need for a biopsy. It is necessary to identify this disorder at the earliest stage and discontinue hydroquinone immediately [99].

Miscellaneous Hyperchromia

Acquired hyperpigmentation of the skin is sometimes interpreted as an adverse effect of drugs (Table 58.4) or secondary to chemical agents (Table 58.5).

Melanocytic lesions are also part of the differential diagnosis of hyperchromic lesions such as melanoma, a subject already discussed in Chap. 17; others are mentioned in Table 58.6.

prickly rash mostly in the midsection, spreading symmetrically (Fig. 58.24).

The cutaneous mastocytosis lesions usually become irritated after suffering friction (Darier's sign, Fig. 58.25). Skin lesions may or may not accompany systemic mastocytosis. Even when the physician considers mastocytosis as a possible diagnosis, it can be difficult to identify because of special technical requirements necessary for a biopsy and because of problems with biochemical testing. The level of serum tryptase is useful to examine the possibility of systemic disease and is mainly used during the initial diagnostic evaluation. Drug therapy stabilizes mast cell membranes to reduce the severity of the attacks and block the action of inflammatory mediators. The primary therapy is histamine H1 and H2 blockers, and the avoidance of triggering factors. While the prognosis for urticaria pigmentosa in early childhood is excellent, with spontaneous resolution in months or years, the disease in adulthood is often persistent [97].

Fig. 58.26 Exogenous ochronosis due to long-term use of hydroquinone to treat dark circles (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

Table 58.4 Other medicines that cause hyperpigmentation

Clofazimine
Amiodarone
Antimalarials
Chemotherapeutics: carmustine, bleomycin, busulfan, cyclophosphamide, dactinomycin, hydroxyurea, methotrexate
Azidothymidine
Diltiazem
Minocycline
Psoralen
Psychotropic drugs
Hormones: oral contraceptives, melanotropic and adrenocorticotropic hormones

Table 58.5 Hyperpigmentation due to metals

Arsenic
Bismuth
Gold
Steel
Lead
Mercury
Silver (argyria)

Table 58.6 Melanocytic hyperchromic lesions

Melanoma
Melanocytic nevus: congenital or acquired
Lentigines
Melanin stains: of lips, penis, and vulva

Vascular and Blood Stains

Purpura

Purpura is mucocutaneous bleeding from blood vessel leakage in the dermis, which measures at least 5–10 mm in diameter, is palpable or nonpalpable, and does not disappear with added pressure. It may have different causes to be investigated, firstly by history and physical examination. Clinical manifestations differ according to the cause, including petechiae (purpura with a diameter less than or equal to 4 mm), contusion, ecchymosis (with generally diameter larger than 1 cm), linear petechiae, and hematoma (shows slight rise, unlike ecchymosis). The color helps determine the etiology, being typically red (hemoglobin saturated with flow and adequate skin perfusion), bright red (superficial bleeding), and blue (restricted blood flow). If there is more hemorrhaging and therefore more swelling and inflammation of the skin resulting from purpura, it is more likely that the lesion is palpable. The retiform purpura is a branched purple complex that indicates microvascular occlusion.

Nonpalpable Purpura

Idiopathic thrombocytopenic purpura is a hematologic disorder characterized by isolated thrombocytopenia without a clinically apparent cause. The major causes of accelerated platelet absorption include immune thrombocytopenia, decreased bone marrow production, and increased splenic sequestration. Its clinical manifestation may be acute, with severe bleeding, mild, or asymptomatic. Treatment should be restricted to those patients with moderate or severe thrombocytopenia who are bleeding or at risk of bleeding [100].

Thrombotic thrombocytopenic purpura is more common in adults, while the hemolytic-uremic syndrome is more common in children. Associated factors are pregnancy, cancer, medications, bone marrow transplantation, and autoimmune diseases. Clinical signs include fever, renal disorders, and changes to the central nervous system. Hemolytic uremic syndrome due to *Escherichia coli* infection is common. The available treatment consists of fresh frozen plasma [101].

Purpura fulminans is a hematologic emergency with skin necrosis and scattered intravascular coagulation. It may progress rapidly and complicate severe sepsis, or may occur as an autoimmune response to otherwise benign childhood infections. The initial appearance of these lesions is well-demarcated erythematous macules that progress rapidly to develop irregular central areas of blue-black hemorrhagic necrosis [102].

A summary of nonpalpable purpuras is provided in Flowchart 58.4.

Palpable Purpura

Any process that occludes or damages the cutaneous vessels results in purpura. When palpable, it may be due to vasculitis or vascular occlusion.

Henoch-Schönlein Purpura

Henoch-Schönlein purpura (HSP) is an acute immunoglobulin A-mediated disorder characterized by a generalized vasculitis involving small vessels of the skin and other organs. It is the most common vasculitis in children, with an incidence of 10–20 cases per 100,000 children per year.
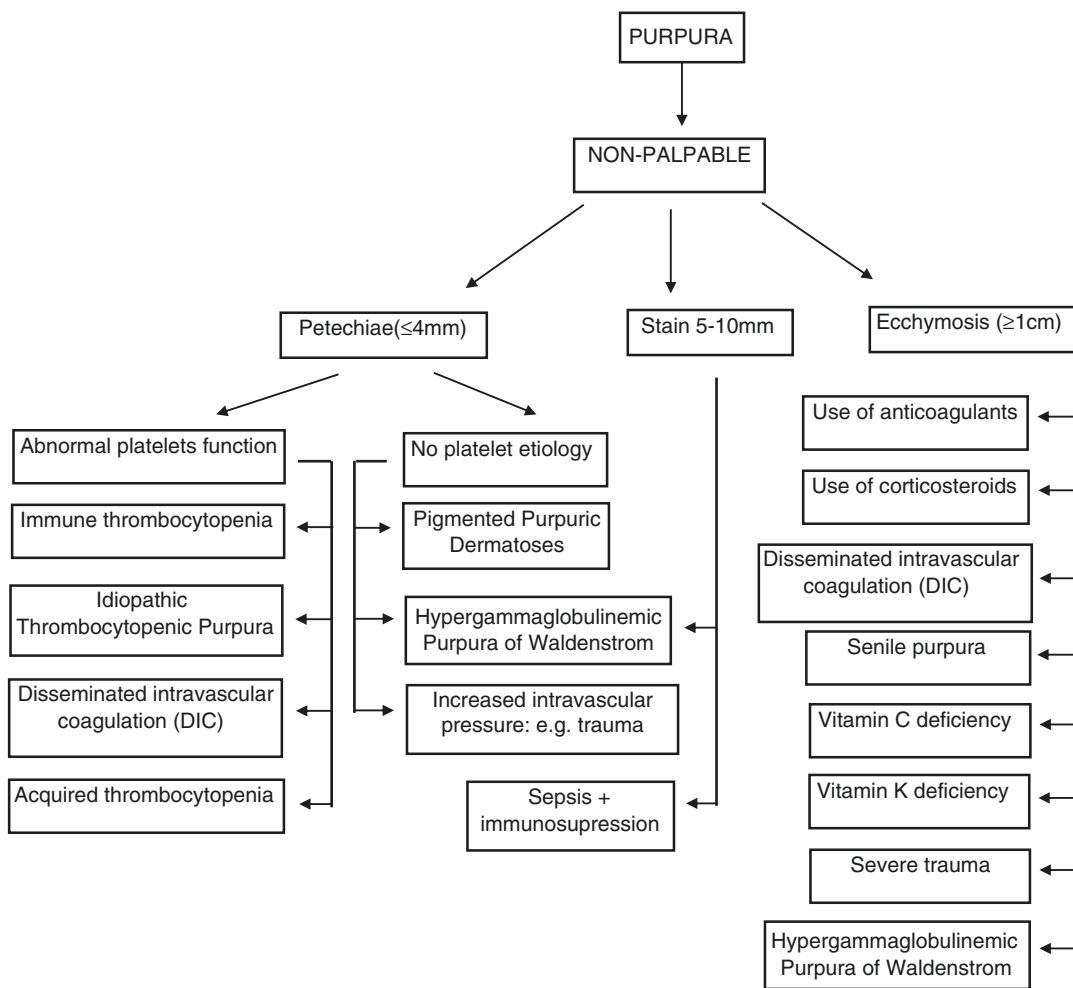
Flowchart 58.4 Nonpalpable purpuras

The etiology of the disease is still not clear and is probably multifactorial. Up to 50% of patients develop the disease after a respiratory infection. Several bacterial and viral infectious agents have been associated with the development of HSP, and some cases have been reported after the ingestion of drugs or vaccines [103].

Generally there are prodromic symptoms such as headache, anorexia, and fever. Subsequently, other developing symptoms may include the following.

Rash (95–100% of cases) is the characteristic feature of the disease, which appears in nearly all patients and usually lasts an average of 3 weeks. Lesions occur on the buttocks and upper thighs in younger children and on the feet, ankles, and lower legs in older children and adults. The primary difference between children and adults is the chronicity and severity of the eruption in adults. The eruption is commonly symmetric and begins as erythematous stains or urticarial lesions, progressing to blanching papules and later to palpable purpura. Usually the face, palms, soles, and mucous membranes are spared. In general, the lesion regresses spontaneously.

The gastrointestinal tract can be involved, with abdominal pain, vomiting, and bloody stools. Other symptoms included arthritis, especially involving the knees and ankles, glomerulonephritis, pulmonary involvement, subcutaneous edema, and scrotal edema [104].

The diagnosis of HSP is clinical. Laboratory tests are usually normal, but sometimes help in the exclusion of other diagnoses and evaluation of renal and hematologic function. Diagnosis is by evidence of immunoglobulin A in the skin or kidney documented by immunofluorescence. The prognosis is generally good, with full recovery and, less commonly, recurrent episodes or persistent disease. This disease does not require specific therapy in the majority of symptomatic cases, except in severe ones that require specific treatments [105].

Pigmented Purpuric Dermatoses

Pigmented purpuric dermatosis is a term used to describe a group of asymptomatic benign eruptions with periods of clinical remission. The lesions present petechiae and pigmentary stains of the skin primarily localized to the lower limbs in the absence of venous insufficiency or hematologic disorders. Their cause is unknown, but several underlying diseases and drugs can be related to the disorder [106].

Pigmented purpuric dermatosis shares common histopathologic features including capillaritis, extravasation of erythrocytes, and hemosiderin deposits. Clinical variations between eruptions lead to subclassification as shown in Table 58.7 [107] (Fig. 58.27).

There is no fully effective treatment. There are several therapies reported, including topical steroids, oral antihistamines, pentoxifylline, and treatment based on UV light [108].

Table 58.7 Pigmented purpuric dermatoses

Schamberg's disease	Usually in women about 50 years
	Insidious onset, in one or both legs
	Irregular reddish-brown stains and asymptomatic
Purpura annularis telangiectodes (Majocchi's disease)	Usually in young women
	Asymptomatic annular spots, telangiectasias and purpura, symmetric, in the lower extremities
Lichen aureus	Usually in young men
	The dermal dense inflammatory infiltrate type band distinguishes golden lichen other pigmented purpuric dermatoses
	Circumscribed areas of papules or yellowish, reddish, or violet stains
	Usually asymptomatic and unilateral (lower extremities)
Itching purpura	Usually middle-aged men
	Abrupt onset, in the lower extremities (can become widespread)
	Reddish-brown stains with intense itching
Gougerot-Blum	Usually in males approximately 40 years
	Primary lesion consists of papule lichenoides polygonal or round, red-brown, in combination with purpura or telangiectasia, in lower extremities
Eczematid-like purpura of Doucas-Kapetanakis	Usually women about 40 years
	Seasonal: spring and summer
	Light peeling on the reddish-brown spots on the lower limbs
	Abrupt onset

Fig. 58.27 Schamberg's disease: irregular *reddish-brown* stains on both legs (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

Raynaud's Phenomenon

Raynaud's phenomenon presents a bilateral cold hypersensitivity and episodic digital color changes in the absence of vascular pathology or digital trophic changes. It affects about 10% of the population, predominantly young women. This condition can be classified as primary (idiopathic) and secondary (known occurrences or because of disease). Vasospasm occurs with exposure to cold, leading to white coloration and severe cyanosis to the fingers, which extends from the fingertips in proximal direction to varying degrees. The distal finger to the line of ischemia is cold, while the proximal portion is warm and rosy. During reheating, the whitish fingers may become cyanotic and then brilliant-red, via reactive hyperemia. Persistent discoloration suggests the secondary cause of disease. Not all patients with Raynaud's present these three color changes [109]. Connective tissue diseases, particularly systemic sclerosis, are most commonly associated with the secondary phenomenon. Current treatment options include general

care, keeping the hands and feet warm, quitting smoking, and avoiding caffeine and stress. In severe cases, the most commonly prescribed class of medications is calcium channel blockers such as nifedipine. If a secondary cause appears, a specific treatment must be applied [110].

Livedo Reticularis

Livedo reticularis is a well-known, relatively common physical dermatologic finding that consists of macular, violaceous, connecting rings that form a net-like pattern, characterized by a cyanotic discoloration or erythematous-cyanotic aspect (Fig. 58.28). It is defined as livedo reticularis when the crosslinked pattern is fully formed with a clear interconnection, with certain areas of the skin within having a normal appearance, even pallor. In livedo racemosa, the crosslinked pattern is not made up of lines that converge and close, and in general is followed by pathologic states. Livedo reticularis is divided into congenital or acquired:
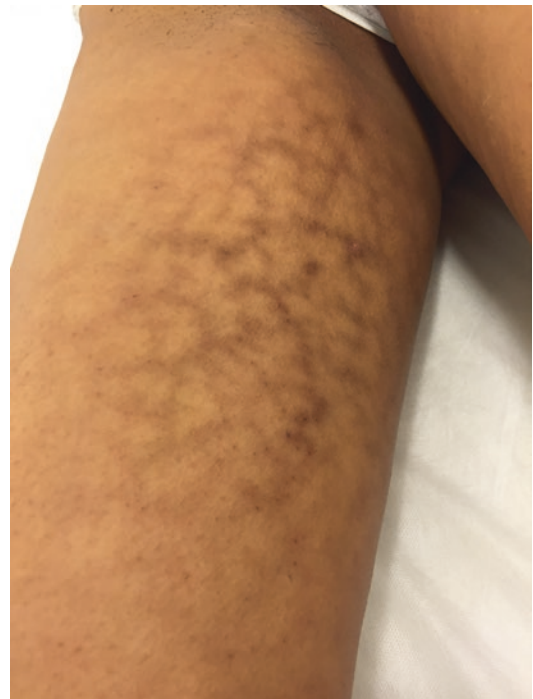
Fig. 58.28 Livedo reticularis: violaceous stains, connecting rings that form a net-like pattern, characterized by a cyanotic discoloration or erythematous-cyanotic aspect (Image courtesy of dermatology service of Federal University of Health Sciences of Porto Alegre – UFCSPA)

Congenital (cutis marmorata telangiectatica congenita): congenital form of livedo reticularis typically presenting at birth, confined to the lower extremities

Acquired: physiologic livedo reticularis or cutis marmorata are synonymous and refer to a normal livedo pattern that occurs in response to cold. It occurs more frequently in neonates, children, and young adults, and can appear in up to 50% of children.

Idiopathic or primary livedo reticularis occurs predominantly in young adults and middle-aged women. Generally it is most widespread, particularly in the lower extremities and sometimes in the upper extremities. Although varying with temperature fluctuations, it continues upon heating. It can manifest with stains, sores, swelling, and numbness. It is a diagnosis of exclusion; it is important to rule out secondary causes, especially in disseminated cases [111].

Livedo reticularis by vasospasm is the most common cause of reticular livedo. It is usually associated with connective tissue diseases and reflects a vasospastic trend, occurring most commonly in patients with Raynaud's phenomenon.

Livedo reticularis racemosa is associated with systemic diseases and is caused by intravascular disorders, disease of the vessel walls, or clogging of vessels (see Table 58.8).

Treatment of livedo reticularis is based on the etiology. The aim of treatment of primary livedo

Table 58.8 Some conditions associated with livedo racemosa

Vasculitis (vasculitis in systemic lupus erythematosus, polyarteritis nodosa, microscopic polyangiitis, Wegener granulomatosis, Churg–Strauss syndrome, vasculitis due to drugs, and others)
Antiphospholipid antibody syndrome
Sneddon syndrome
Thrombophilias
Sickle cell anemia
Myeloproliferative syndromes
Vasculopathy livedoid
Cryoglobulinemia
Calciphylaxis
Hyperoxaluria
Medicines
Infections
Necrosis by coumarin

is to limit exposure to cold, and sometimes it may be necessary to use vasodilators. Livedo racemosa treatment also focuses on the causative disorder [112].

Glossary

Cryotherapy A technique that uses an extremely cold liquid or instruments to freeze and destroy abnormal skin cells that require removal. It can be used to destroy a variety of benign skin growths, such as warts, actinic keratoses, and some malignant lesions (such as superficial basal cell and squamous cell cancers).

Cutis verticis gyrata A condition of the skin of the forehead with hypertrophy and deep vertical folds so as to resemble the surface of the brain. It is a feature of acromegaly, local inflammation, and acute myeloid leukemia. A rare primary form, which affects males only, is associated with neurologic problems.

Darier's sign Skin change produced when the skin lesion in urticaria pigmentosa is rubbed briskly. The area usually begins to itch and becomes raised and surrounded by erythema.

Dermabrasion A technique whereby a dermatome or abrading device is used to remove the epidermis and superficial dermis, allowing regeneration of the epithelium to occur from underlying adnexal structure.

Excimer laser A powerful form of laser which is nearly always operated in the ultraviolet spectral region and generates nanosecond pulses.

Furocoumarins A class of organic chemical compounds produced by a variety of plants. They sensitize the skin to the effects of the sun, thus leading to irregular pigmentation and increasing the risk of sunburn and phototoxicity.

Koebner's phenomenon (isomorphic response) The appearance of new skin lesions on areas of cutaneous injury in otherwise healthy skin, with the same clinical and histologic features as lesions of the patient's original skin disease.

Phototherapy A technique used for the treatment of some skin diseases by exposure to light, including ultraviolet and infrared radiation. It is defined as either medium-

wave light energy (ultraviolet-B light [UVB]) or long-wave light (ultraviolet-A [UVA]). UVB is available as narrowband or broadband.

Wood's lamp Created by Robert Williams Wood, this lamp used especially to detect some skin conditions by the fluorescence induced in the affected areas by ultraviolet radiation.

Zireli's sign Scaling of macules made prominent by stretching the affected skin. It is present in pityriasis versicolor.

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Rash

Isadora da Rosa Hoeffel, Marina Resener de Moraes, and Barbara Lovato

Key Points

- Rashes are the main dermatologic presentation responsible for patients visiting a doctor
- The rash is a sudden skin eruption that usually results from multiple etiologic factors, and exanthem is defined as any eruptive skin rash associated with fever or other constitutional symptoms
- During childhood, infections are the most important cause of rash, and adverse reactions to drugs are the most important cause in adults
- For correct diagnostic elucidation, a complete anamnesis and physical examination are required, as well as identification of the related symptoms and characterization of the rash

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Concept

If a rash is a sudden skin eruption often resulting from an overlying disease, an exanthem is defined as any eruptive skin rash associated with fever or other constitutional symptoms. Usually rashes represent a diagnostic challenge for general practitioners, emergency physicians, and even dermatologists, since different diseases can clinically yield very similar rashes, while the same disease can be differently displayed on the skin [1]. In addition, many of these diseases require prompt and accurate diagnosis for immediate therapeutic management.

The accurate diagnosis of a rash requires detailed anamnesis and physical examination [2, 3]. Data such as patient age, occupation, recent travel, contact with sick people, medication use (ongoing or occasional), immunization status, immunosuppressive condition (drugs, splenectomy, solid-organ transplantation, human immunodeficiency virus [HIV] infection) must be determined. Furthermore, the onset of presentation has to be verified and the presence of associated signs and symptoms, such as fever, cough, rhinorrhea, conjunctivitis, myalgia, arthralgia, headache, gastrointestinal changes, and lymphadenomegaly, has to be questioned. The patient's general condition is another crucial aspect to be determined since some conditions are potentially fatal, for example, meningococcemia, which

evolves rapidly with worsening of the general condition, demanding prompt therapeutic intervention.

Characterization of rash is key to the correct clinical diagnosis. Rashes can be either monomorphic or polymorphic, and many exanthems display exclusive presentation forms. Lesion location can be a major diagnostic clue (e.g., palmar-plantar lesions frequently occur in secondary syphilis). Presence of pruritus is also a key factor in the diagnosis and rules out a great number of diseases. Rash presentation (e.g., papular, vesicular, purpuric rash) is decisive in determining the cause of the rash; therefore, how the basic skin lesions are classified is essential, as are the characterization of the rash according to these definitions and its inclusion into differential diagnosis groups, thus limiting most causes of the exanthem. By describing the patient and the features of the exanthem one can define more or less probable differential diagnoses for each case.

Drug adverse reactions are the main cause of rash and exanthem in the adult population. Infections, usually viral, account for the greater number of these occurrences in the pediatric population [1]. In this chapter the causes of exanthem are divided into adult and pediatric causes to make research and diagnostic clarification easier. However, it is noteworthy that this division is for didactic reasons only, as many diseases, despite their characteristics and frequency in one age range, are not unique for that population, being possible at any stage of life.

Current Condition of the Disease

Rashes are the most common dermatologic sign that lead patients to seek medical attention, regardless of their cause. They are often a major diagnostic challenge because many diseases yield clinically similar exanthems and varied skin manifestations [4]. Despite being less frequent and sometimes rare nowadays, traditional exanthematous diseases, such as measles and rubella, are still prevalent in some countries. Even with the eradication of some of these diseases, new infectious agents are detected and involved in exanthemous presentations each year. Moreover, many diseases with benign behavior, such as infections by some enteroviruses, have been responsible for outbreaks that lead to serious and sometimes fatal forms of exanthematous disease.

Owing to the advance of microorganism detection and isolation technologies, many diseases have had their etiology verified, although many of these diagnostic tests are very expensive and available for research use only. Nevertheless, an etiologic diagnosis should be attempted whenever possible.

Clinical Presentation

Rash is defined as a skin eruption resulting from an underlying disease [1, 2]. Such eruptions can be either localized or diffuse, and display varied clinical forms. Knowledge of the primary skin lesions (Table 59.1) is essential in rash characterization, since one can include each case in a specific group of exanthems, and limit the number of differential diagnoses (e.g., a patient who only displays vesicles is diagnosed with vesicle exanthem and is included in the group of diseases resulting in this kind of eruption).

Table 59.1 Primary skin lesions and their definitions

Macula	Flat nonpalpable lesions, less than 1 cm wide, showing inconspicuous texture and/or color change
Patch	Flat nonpalpable lesions, more than 1 cm wide, showing discrete texture and/or color change
Papule	Circumscribed palpable lesion, above skin surface, less than 1 cm wide
Plaque	Palpable and raised lesion, above skin surface, more than 1 cm wide
Nodule	Palpable raised and indurated lesion usually deeper than the papule
Vesicle	Raised lesion, less than 1 cm wide, with internal light liquid content
Blister	Raised lesion, more than 1 cm wide, with internal liquid content
Pustule	Raised surface lesion with internal yellow content (pus)

Rash: Children

Box 59.1 Etiology of Rash in Children
In childhood, the most important causes are hand-foot-mouth disease, erythema infectiosum, exanthema subitum, scarlet fever, varicella, measles, rubella, Kawasaki disease, staphylococcal scalded skin syndrome, Gianotti–Crosti syndrome, miliaria, and meningococcemia.

Hand-Foot-Mouth Disease

Hand-foot-mouth disease (HFMD) is a highly contagious disease worldwide that usually affects children. It is caused by enteroviruses, mainly the A6, A10, A16 Coxsackie viruses, and the 71 enterovirus. It is transmitted by interhuman contact, the fecal–oral route, or respiratory droplets [5]. Despite an often benign and self-limited evolution, many fatal cases have been recently reported, mostly in Asia [5–7].

Following a 3- to 10-day incubation period, patients start having fever and odynophagia, rapidly followed by the classic presentation of erosive stomatitis mainly in the palate and oropharynx, and a papular-vesicular exanthem in the palmar-plantar region (Fig. 59.1) [6]. The gluteal region and the perineum are also commonly affected, and atypical HFMD cases with papular-vesicular and purpura presentations reaching the scalp, face, arms, and torso have been recently reported and associated with A6 Coxsackie virus infection [7]. The associated symptoms are generally mild, including low to moderate fever, headache, arthralgia, and myalgia. However, during a major outbreak in Singapore in 2000, many patients displayed evidence of pneumonia, meningitis, and myocarditis, some with a fatal outcome [5, 8].

Erythema Infectiosum

Erythema infectiosum, also known as the Fifth Disease, is a very common exanthemous disease in childhood caused by the parvovirus B19 (PB19) and transmitted by contact with respiratory secretions and blood transfusion [9, 10]. After the PB19 infection an inconspicuous

Fig. 59.1 (**a**) Hand-foot-mouth disease. A papular-vesicular rash in the palmar-plantar region. (**b**) Note the vesicle involving the first toe (Courtesy of Ana Elisa Kiszewski Bau, M.D., PhD, Porto Alegre, Brazil)

Fig. 59.2 Erythema infectiosum. "Slapped cheek". The characteristic erythematous rash that affects the malar region of children infected with PB19

prodromal period occurs, characterized by fever and unspecific flu symptoms, followed by skin manifestations. During childhood, the most common clinical presentation includes a macular or macular-papular erythematous rash mostly seen on the face, torso, and limbs. On the face, the noticeable malar rash (Fig. 59.2) is traditionally known as "slapped cheek," and an enanthem in the palatal region can be also noticed. The rash usually becomes more evident when the patient is exposed to the sun during physical activities or heavy heat.

In the adult population, the infection is frequently asymptomatic or with often unnoticed mild symptoms. In symptomatic infections articular involvement is the main clinical presentation, occurring in up to 50% of the involved adult patients. It presents as a form of arthralgia or symmetric arthritis in the patient's hands, and occasionally in the ankles, knees, and wrists [11]. It can mimic clinical presentations of rheumatoid arthritis, and it can even present a positive rheumatoid factor. Cutaneous manifestations in this population show significant variation, which make this a more heterogeneous group regarding signs. The most common presentation is a papular-purpuric eruption on the patient's feet and hands, also known as papular-purpuric gloves and socks

syndrome [12]. Palpable purpuric cases can also be seen, and are similar to the systemic dermatomyositis/lupus erythematosus, acral petechiae, and vesicular pustular rash [13].

A significant manifestation of the parvovirus B19 infection is the transient aplastic crisis. This is a condition whereby a direct invasion of the virus into the bone marrow occurs, and since the PB19 displays tropism by the erythroid progenitor cells there may be destruction of these cells with resulting disruption of red cell production for about 5–10 days. There is no clinical repercussion in healthy patients who show a normal life cycle of red blood cells. In patients with chronic hemolytic anemias, however, such as sickle cell disease and thalassemia, a sudden fall of hemoglobin levels and an acute anemia can occur, thus characterizing the transient aplastic crisis. This acute condition can lead to presentations of congestive heart failure, cerebrovascular accident, and death. Platelet and white blood cell levels can also eventually decrease [14, 15].

Another population at risk for PB19 infection is immunosuppressed patients, such as solid-organ transplant recipients and HIV-infected patients. In these groups the infection period is longer and goes beyond the maximum life cycle of the red blood cells, resulting in acute and chronic anemia [14, 15].

Exanthema Subitum

Largely resulting from infection with the human herpesvirus type 6 (HHV-6) and type 7 (HHV-7), exanthema subitum (also called roseola infantum) is very common during childhood and is characterized by high fever and later onset of cutaneous eruption. It predominantly occurs between 6 months and 2 years of age, with up to 90% of the population being infected over the first 2 years of life; it is transmitted via respiratory secretions [16, 17].

Fig. 59.3 Exanthema subitum. A macular-papular erythematous exanthem on the torso, abdomen, neck, and limbs in a 9-month-old infant (Courtesy of Fabiane Kumagai Lorenzini, M.D., Porto Alegre, Brazil)

The clinical presentation is characterized by high fever (39–40 °C) lasting from 3 to 5 days, often in children being nursed and in good health. This is followed by macular-papular erythematous cutaneous eruption on the torso, neck, and proximal parts of the limbs (Fig. 59.3), when the fever typically subsides. Enanthem of the soft palate and uvula, symptoms of upper respiratory tract infection, otitis media, cervical and occipital lymphadenopathy, and fontanelle vault can be noticed. This latter symptom results from central nervous system involvement, which can result in encephalitis and aseptic meningitis. The most frequent complication of the exanthema subitum includes febrile seizures, present in about 10% of cases [18]. The condition often resolves spontaneously in a few days with no sequelae. A virus reactivation can be seen with immunosuppression [19], and usually occurs with unspecific clinical symptoms such as fever, malaise, and cutaneous rash; however, acute situations, such as hepatitis, encephalitis, interstitial pneumonia, and bone marrow failure, can occur.

Scarlet Fever

Scarlet fever, or scarlatina, is an acute infectious disease caused by the Group A β-hemolytic streptococci (*Streptococcus pyogenes*), a pyrogen-producing bacterium transmitted through saliva and nasopharyngeal secretions and, rarely, through contaminated water and food [20]. It usually infects individuals between 5 and 18 years old, being rare in those younger than 3 years old. The disease incubation period lasts from 2 to 5 days, and transmission begins with the early symptoms [21]. Many people can be asymptomatic carriers, and the individual who develops scarlatina is required to lack both *Streptococcus* immunity (specific-type immunity) and pyrogenic exotoxin immunity [22, 23].

The disease usually starts with a sore throat, associated with high fever, asthenia, anorexia and generalized malaise. Some patients also have vomiting, abdominal pain and convulsions. Around 12–48 h after symptoms onset, patients develop a micro papular exanthem on their torso, cervical region and axillae that disappear under digital pressure. The rough and erythematous skin resembles sandpaper, and petechiae develop in the flexural fold areas, known as Pastia's lines. Facial frontal and malar hyperemia occur in contrast with paleness in the perioral region (Filatov's sign) (Fig. 59.4).

Concomitant with the cutaneous eruption, patients develop pharyngoamygdalitis with purulent exudate, cervical lymphadenopathy, and oral mucosa enanthem. The tongue is initially white, with hypertrophied papillae, after which the white layer detaches, making an erythematous and bright tongue evident, known as "raspberry tongue." Between 7 and 10 days of infection onset, diffuse skin scaling occurs, more intense over the palmar and plantar regions, lasting from 2 to 6 weeks.

Fig. 59.4 (**a**) Scarlet fever. A micropapular exanthem on the torso, cervical region, and axillae. The rough skin resembles sandpaper. (**b**) Filatov sign, the characteristic paleness of perioral region that occurs in contrast to facial hyperemia (Courtesy of Raquel Bonfa, M.D., Porto Alegre, Brazil)

Varicella

Popularly known as chickenpox, varicella is a primary acute and extremely contagious disease characterized by generalized vesicular exanthem on the skin and mucosa. It usually shows a benign, self-limited course, mainly during childhood; however, during adulthood it can have a worse and unfavorable evolution. It results from the primary infection of the varicella zoster virus (VZV), of the Herpesviridae family, transmitted via contact with airborne particles from the upper respiratory tract or contact with lesions of infected patients [24].

The disease incubation period ranges from 10 to 21 days, and the prodromic symptoms generally can be seen from 1 to 2 days before cutaneous eruption. During childhood these symptoms may often go unnoticed; when they occur, their characteristics include low fever, nausea, anorexia, and headache [25]. The rash usually begins on the head, reaching the patient's scalp and face, rapidly spreading through the torso and limbs in a centripetal distribution. Besides pruritus, a very noticeable characteristic is lesion polymorphism; i.e., surface maculae, papules, vesicles, and damaged lesions and crusts are seen practically at the same time (Fig. 59.5) [26]. Airways and mucosa can also be affected. Increases in transaminase levels and thrombocytopenia can also often occur [24]. In general, up to 20 days from symptom onset residual crusts fall off, and the occurrence of secondary infection or early crust removal can yield typical depressing scars.

Although a benign and self-limited evolution occurs during childhood, the disease can have a more acute and symptomatic course during adult life, even in the immunocompetent patient, with high fever, marked exanthem, and possible death, likely resulting from pneumonia. This is the most acute and frequent
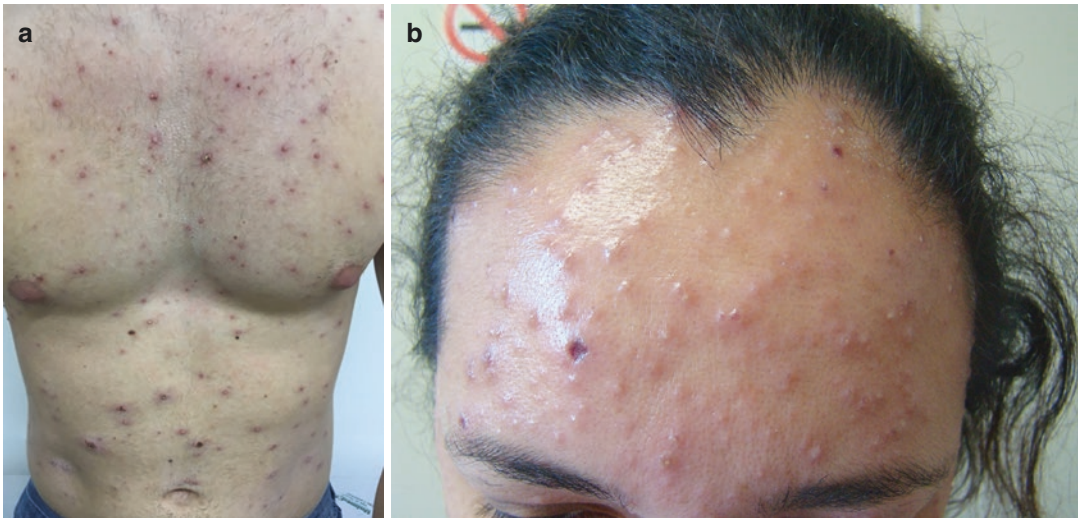
Fig. 59.5 (**a**) Varicella. Lesion polymorphism: maculae, papules, vesicles, and crusts are seen at the same time. (**b**) Vesicles usually begin on the face and scalp

complication, especially in pregnant women, elderly individuals, and immunocompromised patients [24]. Secondary bacterial infection can occur in cutaneous lesions, from simple cases of impetigo to more serious complications, such as cellulitis and erysipelas. Hematologic complications are rare and include leukopenia, fulminant thrombocytopenic purpura, and hemophagocytic syndrome. Involvement of the central nervous system is uncommon, although cerebellar ataxia, meningitis, meningoencephalitis, and cerebral vasculopathy can be seen [24].

Measles

Measles is a highly contagious disease resulting from infection with the measles virus, an RNA virus transmitted through respiratory droplets [27]. Despite the fact that 85% of the children receive at least one dose of the vaccine against measles around the globe annually, the World Health Organization (WHO) estimates that in 2013 there were more than 145,000 deaths from this disease, mostly on the African continent [28]. In many developed countries the disease is still present, and recent outbreaks both in Europe

and the United States, where hundreds of cases were reported in 2015, still show the significance of this disease and its potential morbidity and mortality [29, 30].

Following an early incubation period which lasts from 10 to 14 days, the patient shows prodromic symptoms such as fever, nasal discharge, conjunctivitis, and cough. About 2–4 days from this stage the exanthematous presentation begins, consisting of erythematous maculae and papules, beginning on the forehead (especially along the hair line and behind their ears), progressing in the cephalocaudal direction. The exanthematous presentation recedes in about 3–5 days, disappearing first from the head [31]. Besides the rash, pathognomonic Koplik spots can be noticed: small white lesions in the oral mucosa that can be seen even before the rash.

In noncomplicated cases, the general health condition improves with the emerging rashes. However, up to 40% of patients can develop clinical complications, and presentations tend to be more acute in the very elderly and immunocompromised patients, such as pregnant women and malnourished individuals. The respiratory tract is the most frequently affected location. Pneumonia, otitis media, and tracheobronchitis are the most frequent complications. Besides pneumonia,

encephalitis is also potentially fatal, occurring in about 0.2% of the patients, mainly older children and adults, with a 10% mortality rate. This condition is usually seen 2 weeks after rash onset, presenting with fever, seizures, and variable neurologic changes. Abdominal pain, diarrhea, and elevated liver function tests often occur, despite frank hepatitis being unusual [32]. Contrary to rubella, there are no reports of congenital malformation cases associated with measles, although the typical immunosuppression of pregnancy can more often lead to maternal complications [31].

Rubella

Rubella, also called the Third Disease or German measles, is an exanthematous disease with a viral etiology, transmitted through respiratory droplets, with an often mild self-limited evolution both in children and adults. In 2015 the disease was considered eradicated on the American continent thanks to an extensive immunization program, and since 2009 only imported cases have been reported. However, it still remains a significant cause of congenital malformation, with approximately 100,000 congenital rubella cases around the world each year [33, 34].

Following around 14–21 incubation days, a mild prodromic phase begins, consisting of conjunctivitis, headache, fever, and upper respiratory symptoms. Over 1–5 days a maculopapular exanthem appears firstly on the face, progressing in a cephalocaudal direction. Concomitant with the rash, painful lymphadenopathy on the occipital, retroauricular and cervical regions is seen, often persisting for many days. After 3 days, in general, the skin eruption tends to disappear following the initial presentation order [33].

Complications in adults and children include arthralgia, arthritis, hepatitis, myocarditis, pericarditis, hemolytic anemia, and thrombocytopenic purpura [31]. The major danger presented by rubella is infection in a nonimmune pregnant woman over the first trimester, when there is a risk for the virus to be transmitted to the fetus and the consequent development of congenital rubella syndrome.

Kawasaki Disease

Kawasaki disease (KD) is an acute systemic vasculitis mainly affecting children younger than 5 years. Despite many studies, the etiology remains unknown [35], although the infectious etiology theory is the most accepted nowadays. No agent has yet been isolated, but the disease shows seasonal variation, is seldom seen in children being nursed under 6 months, and has infrequent recurrences. The main concern regarding the disease is that it represents the main cause for acquired heart disease in developed countries, and it is estimated that aneurysms or ectasia of the coronary arteries develop in up to 25% of nontreated patients [36].

The clinical manifestations of KD are also used as the diagnostic criteria [37, 38]. They include at least five of the six conditions described in Table 59.2.

The exanthem is usually polymorphic and seen up to the fifth day of the disease. It has no pruritus, and shows variation from maculopapular erythematous-like and diffuse lesions, the most usual form, to the hives-like form, scarlatina-like form, erythrodermic-like form, purpuric-like form, erythema multiform-like form, and, rarely micropustules on the limb extensor surfaces [36]. It is often seen on the trunk and limbs, with

Table 59.2 Diagnostic criteria for the Kawasaki disease. At least 5 out of the 6 mentioned findings are necessary to make the diagnosis

1. Fever lasting more than 5 days
2. Bilateral conjunctive and nonpurulent inflammation
3. Limb changes, such as erythema and/or edema on the hands and/or the feet during the acute phase, as well as scaling of the digital pulp during the recovery phase
4. Cervical lymphadenopathy
5. Lips and oral cavity changes such as edema, erythema and lip cracks, raspberry tongue, and oropharyngeal hyperemia
6. Polymorphous exanthem

noticeable preference for the groin and perineal regions.

Organs other than the skin can also be attacked by vasculitis. During the acute phase, besides the diagnostic criteria, arthritis and arthralgia (30%), uveitis (17%), diarrhea (15%), hepatic dysfunction (10–25%), aseptic meningitis (10–25%), and later on neurosensory deafness can occur. However, heart impairment is the major concern regarding cases of KD. Its most usual form involves the coronary arteries, affecting 15–25% of the nontreated patients, and includes aneurysms, ectasia, and stenoses of the coronary arteries, which can lead to acute myocardial infarction. Moreover, myocarditis, pericarditis, endocarditis, and heart valve and coronary damage, with hemodynamic repercussion and a 2% mortality rate can occur [36].

Staphylococcal Scalded Skin Syndrome

The staphylococcal scalded skin syndrome (SSSS) is an infectious and exfoliative disease that affects mainly newborns and children younger than 6 years, and eventually adults (especially immunodepressive or chronic renal failure patients) [39]. The disease is part of an infection range mediated by toxins produced by the *Staphylococcus aureus* bacterium. Most cases of SSSS are caused by exfoliative toxin types A and B, which affect the epidermis granular layer, specifically in the desmoglein glycoproteins 1, and cause their disruption, with the resulting sterile skin blistering and exfoliation. Despite a good prognosis in childhood, with a mortality rate of about 3–4%, this rate increases in adulthood to more than 60% [40].

The disease often presents a prodromal phase characterized by fever, irritability, odynophagia, hypersensitivity, and skin discomfort [41]. A light macular rash begins and quickly progresses to an orange-erythematous color to become confluent, swollen, and scaly. Periorificial, flexural, and friction skin areas wrinkle with blistering and scaling. The Nikolsky sign, a slight friction on the perilesional skin and consequent detachment of the most superficial skin layer, is positive. Another distinctive characteristic is the presence of radial fissures, periorificial crusts, and varying facial edema (Fig. 59.6). One or 2 days after their appearance, the blisters and the perilesional skin detach, and areas of thin

Fig. 59.6 (**a**) SSSS. Flexural skin areas with blistering and scaling. (**b**) Characteristic radial fissures, periorificial crusts, and facial edema

and moist skin of varying sizes remain. Often the primary focus of the *S. aureus* infection is not identified, although some patients can present rhinorrhea, conjunctivitis, or other skin pyogenic foci.

Gianotti-Crosti Syndrome

The Gianotti-Crosti syndrome (GCS), also known as infantile papular acrodermatitis, is a rare disorder, characterized by a papular exanthem affecting mainly the face and limbs of children from 6 months to 14 years old. It is seen as a cutaneous reaction self-limited to many infections, mainly the viral ones, and to some vaccines [42]. The main virus already related to GCS are the Epstein–Barr virus the HHV-6, parvovírus B19, cytomegalovirus, A and B hepatitis viruses, syncytial respiratory virus, and rubella virus.

Commonly the GCS is preceded by mild constitutive symptoms, such as fever, lymphadenopathy, and upper respiratory symptoms, followed by a sudden eruption of erythematous or brownish, sometimes lichenoid, asymptomatic, monomorphic papules, symmetrically distributed throughout the face, the gluteal region, and the limbs (Fig. 59.7), with some patients showing lesions reaching the torso, or limited to the face [43, 44]. A high erythrocyte sedimentation rate, as well as lymphocytosis with atypical lymphocytes in the hemogram, is apparent in some patients. Lesions spontaneously disappear in 2–8 weeks, and cases persisting for up to 6 months are uncommon.

Miliaria

Miliaria is a disorder that affects the eccrine sweat glands, generally occurring as a result of high moisture and heat. On such occasions the
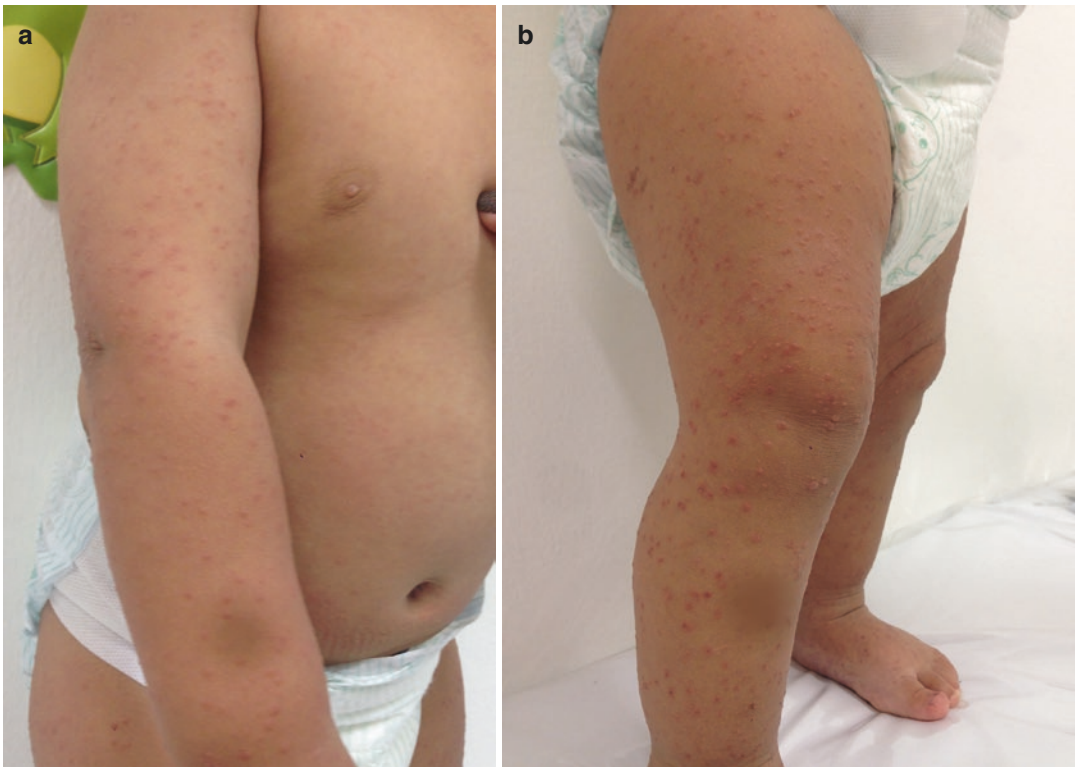
Fig. 59.7 (**a**, **b**) Gianotti–Crosti syndrome. Erythematous and lichenoid papules symmetrically distributed throughout the limbs

Fig. 59.8 Crystalline miliaria in a newborn. Numerous micropapules and microvesicles

eccrine ducts become obstructed at different skin depths. It can be often found in young children, mainly newborns, whose ducts are not totally formed, but can be also found in adults who live or work under hot and moist conditions. Often the condition develops after episodes of fever, and some drugs have also been associated with miliaria development [45].

There are three basic types of miliaria. In crystalline miliaria, the ducts are obstructed at the corneal stratum level, and tiny vesicles of transparent content can be seen mainly on children's and adults' face and upper torso (Fig. 59.8); they are easily disrupted. Miliaria rubra is characterized by duct obstruction at the level of the mid epidermis layer, and is the most common subtype. It manifests as small papules and erythematous plaques, covered by punctiform vesicles mainly found on the cervical region and the torso. It can cause pruritus and itching, sometimes with sterile pustules [46]. When the miliaria rubra is relapsing or chronic it can result in the third type of miliaria, known as miliaria profunda. In this case a duct obstruction occurs at the dermoepidermal junction, and although asymptomatic the patient is at significant risk for thermoregulation problems [47].

Meningococcemia

Caused by the *Neisseria meningitides* bacterium, meningococcemia is an acute and potentially fatal disorder that mainly affects small children (6 months to 1 year old), and young adults worldwide. The infection is most frequently seen in the winter and the beginning of spring, occurring more in males than females. It is already known that patients with congenital or acquired immunodeficiencies, as well as asplenic patients, carry a greater risk for the development of meningococcemia [49, 50].

About 1–14 days after contamination and development of the bacterium in the nasopharynx, the prodromal symptoms of fever, anorexia, nausea, vomiting, torpor, headache, arthralgias, myalgias, and limb changes (cold and violet-like) begin. Nuchal rigidity is typically absent, contrary to cases of meningococcal meningitis. A usual occurrence and one which may immediately raise meningococcemia suspicion is the quick evolution of sepsis, characterized by high fever, tachycardia, tachypnea, and eventual hemodynamic instability.

However, the key manifestation is cutaneous: up to half of the patients display a petechial and purpuric eruption; fewer patients can also develop an inconspicuous and transient morbilliform rash on the torso [51]. The major concern regarding meningococcemia is its progression to disseminated intravascular coagulation, known as purpura fulminans. The petechiae, in these cases, progress to hemorrhagic blisters, ecchymoses, ischemic necrosis of the limbs, and adrenal gland hemorrhage and hypotension. The prognosis of such patients' is reserved, and death can occur within 24 h even when patients undergo amputation of the affected limb.

Table 59.3 lists the main differential diagnoses of rashes in childhood and their key characteristics.

Table 59.3 Main differential diagnoses of rashes in childhood and their key characteristics

Disease	Incubation	Exanthem/related symptoms	Key characteristics/diagnosis
Hand-foot-mouth disease	3–10 days	Low fever and odynophagia followed by erosive stomatitis and papular-vesicular exanthem on palms and soles	Good general condition Gluteal and perineal regions also frequently attacked Clinical diagnosis
Erythema infectiosum (fifth disease)	5–4 days	Discrete prodromal period followed by macular or macular-papular, erythematous exanthem that is seen mainly face, torso and limbs, worst in exposed-to-light areas	Exuberant bilateral malar rash, known as "slapped fascia" In the adult population, the most often seen presentation is a papular-purpuric eruption on their feet and their hands, known as "papular-purpuric gloves and socks syndrome," related to arthralgias IgM + parvovirus B19
Exanthema subitum (roseola infantum or sixth disease)	10–15 days	High fever lasting from 3 to 5 days in <3 years, with no other symptoms Abrupt fever recession when macular-papular erythematous exanthems appear on the torso, neck, and upper and lower limbs' proximal parts	High fever (>39 °C) in babies being nursed, in good general health condition Fever recession concomitant of the rash emergence IgM + HHV-6, or HHV-7
Scarlet fever (scarlatina)	2–5 days	High fever + odynophagia + general malaise Micropapular erythematous diffuse exanthem, with rough and scaly skin, resembling "sandpaper"	Pastia sign: linear petechiae in flexural areas Filatov sign: perioral paleness "raspberry tongue" Oropharynx culture or serum antibody detection (e.g., ASLO)
Varicella	10–21 days	Rash usually starts on the face and scalp, rapidly progressing onto the torso and limbs Presence of vesicle on erythematous papule	A remarkable rash feature is the lesion polymorphism: excoriated macular, papular, vesicular surface lesions; excoriated pustules, crusts, and lesions seen virtually at the same time PCR / IgM + varicella zoster
Measles	10–14 days	Prodromes of fever, coryza, conjunctivitis, and cough Erythematous maculae and papules start on the face, mainly at the hair line and retroauricular region, progressing to a cephalocaudal direction. They remain for 5 days at least. Light scaling can occur	Koplik spots: small white lesions on the mucosa (can be seen even before the rash) IgM + measles/increase at least 4× of the IgG titter
Rubella	14–21 days	Mild prodromes of conjunctivitis, headache, fever, and respiratory symptoms Macular-papular erythematous exanthem starting on the face, in cephalocaudal progression	Painful lymphadenopathy in the occipital, retroauricular, and cervical regions PCR oropharyngeal secretions, urine, blood, or liquor Specific IgM + /increase of at least 4× of the IgG titter
Kawasaki disease	Not known	Fever for at least 5 days 1. Polymorphous exanthem 2. Bilateral conjunctival nonpurulent inflammation 3. Limb alterations 4. Cervical lymphadenopathy 5. Lips and oral cavity changes	Very frequent heart impairment ECG + echocardiogram Clinical diagnosis: fever + 4 of the 5 previously described findings

Table 59.3 (continued)

Disease	Incubation	Exanthem/related symptoms	Key characteristics/diagnosis
SSSS	48 hours average	Fever, bad mood, odynophagia, discomfort, and skin hypersensitivity Erythematous-edematous scaly rash	Skin hypersensitivity Radial fissures and periorificial crusts Noticeable impairment of the flexural areas Nikolski sign +
Meningococcemia	1–14 days	Fever, lack of appetite, vomiting, torpor, headache, cold extremities There can be morbiliform discrete transient rash on the torso, followed then by the typical petechial and purpuric eruption	Sudden onset and quick progression into sepsis PCR/bacteriologic/blood, cutaneous lesions, and liquor bacterioscopy to identify the *N. meningitides*
Gianotti-Crosti syndrome	Variable	Sudden eruption of erythematous or mousy, monomorphic, and asymptomatic papules	Noticeable symmetrical extremities impairment: face, gluteal region, and limbs There is no specific test
Miliaria	Not known	Miliaria rubra is the most frequent and clinically important Small papules and erythematous plaques, covered by a punctiform vesicle involving predominantly the cervical region and the torso	Related pruritus and/or itching History of excessive sudoresis or heat and moisture exposure

Rash: Adults

> **Box 59.2 Etiology of Rash in Adults**
> The main causes of rash during adulthood discussed in this chapter are drug eruptions, contact dermatitis, syphilis, and the emerging dermatologic viral diseases.

Drug Eruptions

Adverse drug reactions usually occur on the skin and are the main cause of diffuse rash in the adult population [1]. These reactions are often unexpected and occur in 2–3% of the general population, increasing to 10–20% in nosocomial environments [52, 53]. Most of them have a benign course, although they can also lead to significant morbidity and even death in the most acute cases, with rates varying from 0.2% to 29.3% depending on the study [54].

The most usual mechanism of action is tardive hypersensitivity. The administered drug is processed and promoted to the Langerhans cells, acting as haptens and inducing the cellular and humoral response. The drug-triggered process can be either unexpected or a genetic or acquired predisposition

Table 59.4 More commonly involved drugs in pharmacodermias

Class	Commonly involved drugs
Antibiotics	Penicillins Sulfamethoxazole Cephalosporins Quinolones Isoniazid
Antipyretics/anti-inflammatories	Acetylsalicylic acid Sodic dipyrone Acetaminophen Sodic dicoflenac and diclofenac potassium Piroxicam
Anticonvulsants/antidepressives	Barbiturates Valproates Carbamazepine Phenytoin Lamotrigine
Antihypertensives	Furosemide Thiazíds
Others	Allopurinol Oral contraceptives Propiltiouracil

by the individual, and the most commonly involved drugs are antibiotics, anti-inflammatories, and anticonvulsants [55, 56] (Table 59.4).

Some risk factors were found in research studies, most of them involving an unexpected response in patients older than 60 years,

women, and obese individuals. It is more often seen in patients with autoimmune diseases or with an active viral infection who have been given high doses of drug, although the reactions are not necessarily dose-dependent [57, 58].

When facing a rash in an adult patient a possible pharmacodermia must always be considered. Exanthems are the most usual clinical form of polymorphic manifestation as erythematous macules that can be associated with small papules. At first, the lesions are seen on the torso and upper limbs and can then become confluent, with an unaffected mucosa in most cases. Pruritus and low fever are usual [59].

The rash usually occurs between the first and the second week after drug administration, or even some days after drug interruption; therefore, it is important to list all the drugs used and, if possible, in chronological order. Patients using many drugs make the identification of the causative drug difficult, and often the patients cannot recall the drugs they use or do not mention drugs they sometimes take (not on a daily basis) such as analgesic and anti-inflammatory drugs.

Some clinical aspects signal more acute reactions, such as facial edema, peripheral hypereosinophilia, mucosal lesions, and painful or grayish lesions [60]. These presentations can lead to considerable morbidity and mortality requiring hospital admission. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, acute generalized exanthematous pustulosis (AGEP), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) are among the most acute presentations (Figs. 59.9 and 59.10).

DRESS syndrome is often triggered after the first use of the drug. Erythematous mac-

ules with superficial pustules upon them are apparent, as well as facial edema in certain cases. Many organs are also affected, simultaneously or after the skin manifestations, frequently represented by significant peripheral eosinophilia and higher hepatic enzyme levels. Patients usually show fever and lymphadenopathy during physical examination. When the drug is discontinued the symptoms can still be seen for some weeks. Only seven classes of drugs can trigger this syndrome: anticonvulsants, sulfonamides, allopurinol, nevirapine, abacavir, dapsone, and minocycline [61, 62].

The SJS and TEN are extremely acute forms of drug reaction with a high mortality rate. From 1% to 10% of the skin in SJS and more than 30% in TEN are affected by detachment of the skin. The rash can begin as macules that develop into papules, vesicles, urticarial plaques, confluent erythema, and often bullae. After detachment of the skin, it becomes susceptible to secondary infection. Mucosal lesions are usually displayed, as well as fever and variable systemic changes. The most common causative drugs include allopurinol, anticonvulsants, antiretrovirals, anti-inflammatories, and antibiotics [61, 62].

Acute generalized exanthematous pustulosis (AGEP) usually begins 48 h after drug use. Clinically it shows hundreds of sterile nonfollicular pustules mainly on the torso and intertriginous areas associated with pruritus. When the mucosa is involved it occurs only in one area (the most usual sites include the mouth and the lips). It presents systemic symptoms associated with fever, leukocytosis, and renal, pulmonary, and hepatic dysfunction. Mortality rate is less than 5% [62].
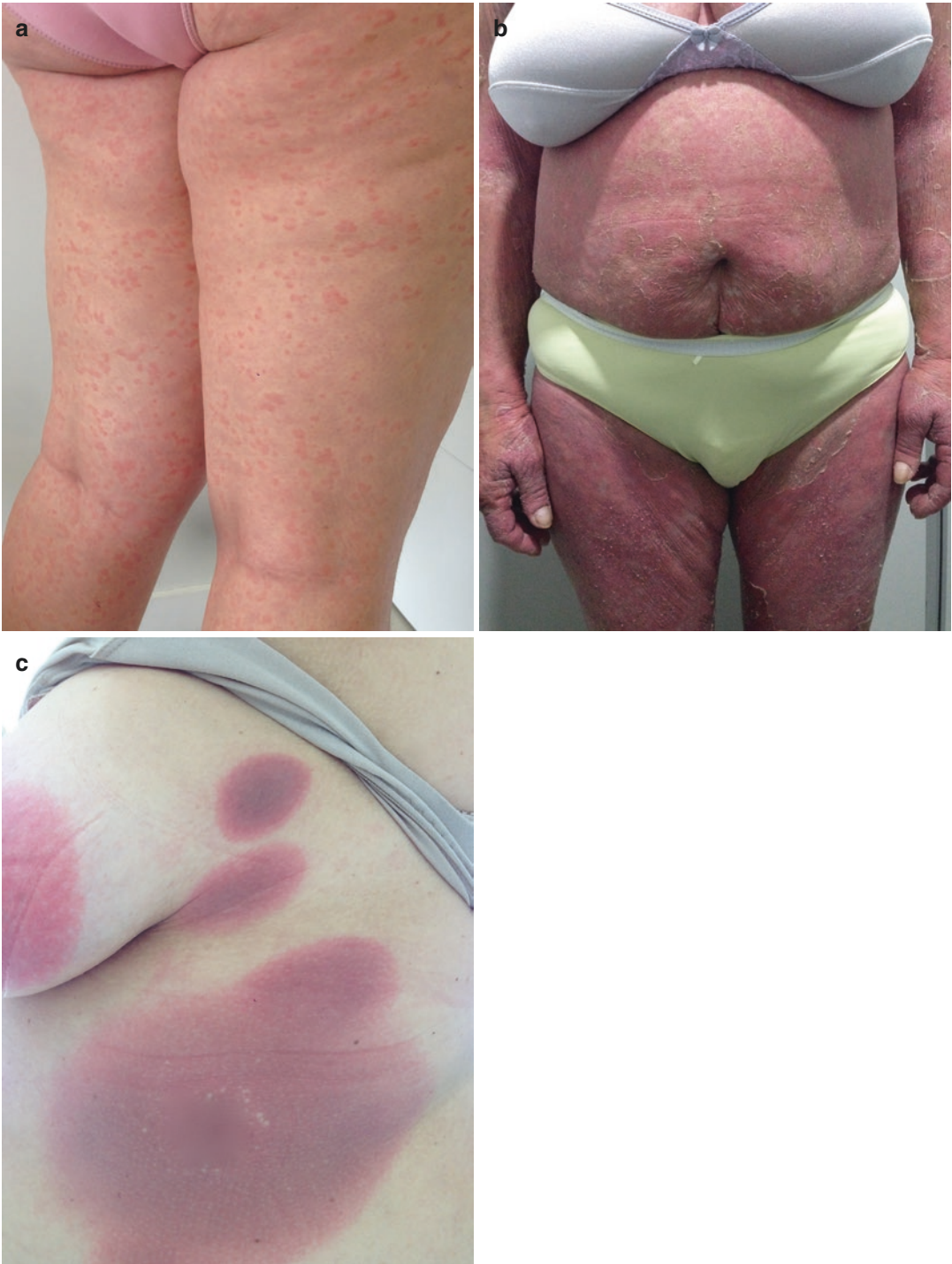
Fig. 59.9 (**a**) Urticarial rash from oral codeine. (**b**) Diffuse erythema and desquamation of skin resulting from ingestion of diclofenac. (**c**) Fixed drug eruption. It is a special type of pharmacodermia, and characteristically recurs in the same site or sites each time a particular drug (in this case ibuprofen) is taken

Fig. 59.10 (**a**) DRESS due to phenobarbital. Diffuse involvement of the face, trunk, and upper limbs. (**b**) NET. Target lesions progressing to bullae. (**c**) SJS. Mucosal erosions

Contact Dermatitis

Contact dermatitis is an inflammatory response in skin resulting from contact with external agents. It occurs in about 15–20% of the population, being rare in children. Regarding etiopathogenesis, contact dermatitis is classified as: (1) irritant contact dermatitis; (2) allergic contact dermatitis; (3) phototoxic contact dermatitis, and (4) photoallergic contact dermatitis. In daily clinical practice the most relevant forms include allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD) [64, 65].

ACD is a delayed-type hypersensitivity reaction (Gell–Coombs type IV), resulting from

repeated exposure to the allergen after individual sensitization at the first contact. For example, contact dermatitis to chromium and cobalt (found in cement) has been identified in building construction workers. With regard to photoallergic contact dermatitis, the concomitant presence of allergen and radiation is necessary to trigger the immunologic process.

ICD accounts for up to 80% of contact dermatitis cases; it can result from a single or a repeated exposure to aggressive agents, triggered by direct damage caused by the chemical agent, for which the action does not have the participation of immunologic events. A classic example is the individual inadvertently coming into contact with solvents, detergents, and acids used in industry. Similar to ACD, in phototoxic contact dermatitis there is no immunologic response but, in order for it to occur, the susceptible individual must be exposed to a sufficient amount of agents and light. This latest example can be seen, for example, when a patient has contact with lemon juice or leaf before being exposed to solar radiation. Apart from the type of contact dermatitis, this condition is affected by the triggering chemical substance and the length and the nature of the contact, besides individual predisposition [65, 66].

The clinical manifestation depends on contact type and place, duration of exposure to the allergen, and evolution (Fig. 59.11). The initial phase corresponds to acute eczema, characterized by erythema, edema, papules, vesicles, and even blisters. There is a prevalence of only erythema and edema on specific sites, such as the eyelids and the genital area. In ICD, depending on the contact route, lesions can display necrosis; they

Fig. 59.11 (**a**) Irritant contact dermatitis due to contact with the *Euphorbia milli* plant. (**b**) Acute eczema characterized by edema and erythema due to ketoconazole shampoo. (**c**) Lichenified erythematous plaque characteristic of chronic contact dermatitis to nickel (note the lesion restricted to the belt contact area)

usually occur where the substance exposure occurred, although it can follow a diffuse route in ACD. The irritant form is more common in children and is usually on the legs, hands, and face.

In subacute eruptions, the presence of exudation and crusts is noticed; the chronic form occurs when the contact continues, or the dermatitis remains even without contact. It is characterized by lichenified erythematous plaques, peeling and, eventually, fissures, with pruritus as the main symptom. There is no trend to disseminate, being restricted to the substance contact areas. In ICD it usually occurs in locations experiencing light friction trauma [66, 67].

Pityriasis Rosea

Pityriasis rosea (PR) is an acute inflammatory skin disease of benign and self-limited evolution, characterized by distinctive lesions on oval and desquamative plaques. It usually affects patients

from 10 to 35 years old, with an estimated prevalence of 0.3–1.4% of the general population. Its etiology is still unknown despite many studies suggesting an infections or reactive cause [68].

In its classical presentation, the disease is characterized by the appearance of an initial lesion known as the "herald plaque" or "mother patch," consisting of an oval or round, erythematous–squamous single plaque of centrifugal growth, with a diameter of 2–10 cm. The center of the "mother patch" tends to be lighter, with the outer edge showing a more conspicuous erythema and a thin, scaling peripheral collarette. About 7–14 days after the onset of the "mother patch" the period known as secondary rash or eruptive period begins, when multiple lesions similar to the "mother plaque" appear, smaller but in great quantity, spread over the torso, neck, and limb root (Fig. 59.12). On the torso, the lesions often spread along the skin cleavage lines, giving the typical aspect of a "Christmas tree" pattern. Pruritus is a common symptom of PR, although of low intensity [69]. A few patients
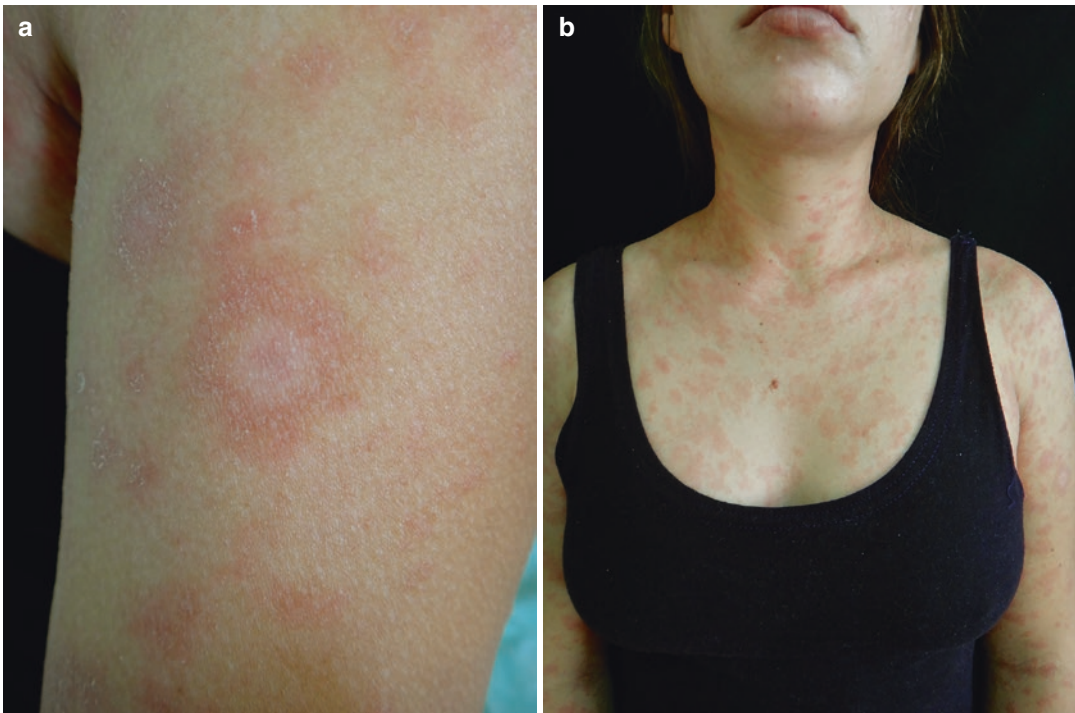
Fig. 59.12 (**a**) Pityriasis rosea. "Herald plaque" or "mother patch." An oval erythematous-squamous single plaque of centrifugal growth, with the lighter center and the outer edge showing a more conspicuous erythema and a thin scaling peripheral collarette. (**b**) Secondary rash of pityriasis rosea (note the herald plaque in the left arm)

develop atypical presentations, such as uncommon distribution, long evolution, rash recurrence, and absence of the mother patch, ranging from mild cases to severe symptoms. Generally the secondary rash spontaneously recedes in 2–4 weeks, with a mean total disease duration of 5–8 weeks [70], with remission with no sequelae.

Secondary Syphilis

Syphilis is a contagious disease caused by the *Treponema pallidum* spirochete; its incidence is worldwide and has shown a steady increase over the second half of the twentieth century, mainly in men with other men as sexual partners [71, 72]. It is transmitted through sex or intrauterine (vertical transmission), and estimates point to about 10.6 million cases a year, most of them in developing countries [73]. Traditionally syphilis is divided into the primary stage (chancre), secondary stage (syphilitic roseola and syphilides), latent period (asymptomatic), and tertiary stage (gumma, neurosyphilis, and cardiovascular, hepatic, renal, or bone lesions). Another classification, which considers treatment, degree of infectivity, and risk for neurologic involvement, organizes the clinical presentations into two major groups, early syphilis and late syphilis [73, 74], a division that also determines the treatment according to the WHO (Table 59.5). Here we focus only on secondary syphilis, since it is a significant differential diagnosis of rashes in the population.

Around 6–8 weeks after the appearance of the primary chancre the secondary manifestations of the disease arise, which result from the spread of the hematogenic pathogen. This secondary phase is characterized by a roseoliform exanthem which shows nonconfluent erythematous macules with little pruritus, usually on the torso, periumbilical region, and internal surfaces of the limbs, rapidly spreading throughout the rest of the body. The lesions are pink to chestnut red in color and eventually can be lightly raised or itchy. Concomitantly generalized adenopathy is noticed. The exanthem is self-limited, and disappears some days or weeks later, possibly leaving some residual hyperpigmentation. A new eruption can arise 3–6 months after appearance of the chancre: they are small, raised, pink- or coppery-colored infiltrating papules that are hard to the touch [74–76]. Papules can be smooth or show an adhered scale which may display a peripheral scaling collarette if more noticeable (Biett collarette). Those lesions are mainly seen on the face, torso, cubital fossa, and popliteal region, although they may affect other parts of the body. Characteristically palmoplantar, red-yellowish, painful macules and papules are noticed (Fig. 59.13). Less often seen are pustulous lesions, and flat or raised plaques known as condyloma lata. Around 5% of secondary syphilis is accompanied by an irregular alopecia, and nearly one-third of patients display a related mucous involvement. Typical syphilis mucous lesions consist of round and flat erosions covered with a grayish membrane, possibly found in the oral cavity or the genital region. Not uncommonly the patient may have pharyngitis, tonsillitis, laryngitis, or areas on the tongue devoid of gustatory papillae. Secondary syphilis lesions may fall into remission after treatment or spontaneously when the recurrence rate can reach 25% [74–76]. After lesion disappearance the disease begins a clinical latency stage, although serologic tests remain positive.

Table 59.5 Syphilis division into early and tardive forms and respective treatments

Classification	Clinical forms	Characteristics	Treatment
Early syphilis	Primary stage Secondary stage Early latent stage	High infectivity Low risk for neurological sequelae	Benzathine benzylpenicillin 2.400.000 UI, by intramuscular injection, at a single session (because of the volume involved, this dose is usually given as two injections at separate sites)
Late syphilis	Late latent stage Tertiary stage	Low infectivity High risk for neurological sequelae	Benzathine benzylpenicillin 2.400.000 UI, intramuscular, once weekly for 3 consecutive weeks Aqueous benzylpenicillin 12–24 million UI by intravenous injection, administered daily in doses of 2–4 million IU every 4 h for 14 days

Fig. 59.13 (**a**, **b**) Secondary syphilis. Roseoliform exanthem. (**c**, **d**) Typical palmoplantar lesions of secondary syphilis

Emerging Dermatologic Viral Diseases

Recently diseases thus far displaying an essentially benign character have become a more acute problem in public health, resulting in global actions by the scientific community and the WHO. This section focuses on the three main recently emerging dermatologic viral diseases: dengue fever, Zika, and chikungunya. These are all diseases basically transmitted by the bite of a mosquito belonging to the *Aedes* species (mainly *A. aegypti* and *A. albopictus*), although vertically transmitted (mother–baby), blood and sexually transmitted cases have been reported. The mosquito has diurnal and domestic habits, lives inside people's homes, and feeds on human blood, mainly during early morning and early night. Reproduction takes place in clean and still water through the female's oviposition, and only females bite the humans.

Dengue fever results from the DEN-1, DEN-2, DEN-3, and DEN-4 serotypes of the dengue virus, an RNA virus of the Flaviviridae family. The disease infection may vary from asymptomatic to acute forms, and even death, all depending on the host and the virus conditions. Estimates nowadays refer to 50–100 million dengue fever cases a year in the world [77]. In addition, the viral infection does not guarantee permanent protection, and the same patient may be repeatedly infected [78]. Traditionally the disease is divided into dengue fever and dengue hemorrhagic fever. In classical dengue fever, after the 5- to 7-day average incubation stage there is abrupt fever onset, general malaise, arthralgia, myalgia, and retro-orbital pain. Cephalea, nausea, vomiting, and cutaneous manifestations are usual findings. Cutaneous involvement is seen in 50–80% of the patients, usually as a patchy exanthematous eruption on the face, neck, and torso, coincident with the fever or not. Maculopapular eruption is also frequent, mainly on the torso. Small petechiae and ecchymoses can also occur, mainly in the conjunctiva and the palatum, although they are more often found in dengue hemorrhagic fever, the most severe form [79]. Dengue hemorrhagic fever has an onset similar to that of classical dengue, but evolves with high fever and hemorrhagic phenomena, secondary to an increase in vascular permeability, plasma extravasation, thrombocytopenia, platelet function changes, and disseminated vascular coagulation. Multiple petechiae and ecchymoses are often seen, as well as cavitary effusions, gastrointestinal bleeding, hepatosplenomegaly, and circulatory failure.

Besides dengue fever, another virus transmitted by the *Aedes* mosquito species is the Zika virus, which also belongs to the RNA type of the Flaviviridae family. It was named after the place where it was found for the first time, the Zika Forest, in Uganda, in 1947. Only 20% of the virus-infected patients develop a clinically evident disease, and the absolute majority of infected patients show a mild form of the disease, with symptom disappearance over 3–7 days. Cephalea, low fever, arthralgias, cutaneous rash, pruritus, and conjunctival erythema are the main symptoms. Other less frequent symptoms include limb edema, odynophagia, coughing, and vomiting. The rash displayed in most of the patients is generally maculopapular and erythematous, predominantly involving the torso and the upper limbs. Despite the usually benign course of the disease, it has recently been given great relevance because of a suspected association of the infection with pregnant women and the possible occurrence of microcephaly in newborn babies. At the end of 2015 Brazil registered a very significant increase of microcephaly cases, mainly in the northeast region where, at the beginning of the year, many Zika cases were registered. Initially the presence of viral RNA in the amniotic liquid was shown in two fetuses with microcephaly, an event consistent with intrauterine viral transmission [80]. More recently, the presence of the virus in the brain of a fetus with acute microcephaly was shown, whose mother had been in Brazil by the end of the first gestational trimester and had developed a clinical presentation compatible with the Zika infection. In that report the virus had not been found in any other fetal organ but the central nervous system, and its genome was totally recognized and decoded. A difference in the sequence of two amino acids in relation to the previously known sequence was observed in the viral genome, something that may be merely an accidental event or a virus adaptation to the new environment [81].

Certainly new studies are necessary to confirm such an association. Another significant fact is that, just like dengue, cases of neuropathies and Guillain–Barré syndrome were also associated with Zika infection, a still unproven fact.

The third emerging dermatologic viral disease results from an RNA alphavirus of the Togaviridae family and causes a disease named after it: chikungunya. Just like dengue and Zika, it is transmitted by the *Aedes* species of mosquitoes, and following the incubation stage from 2 to 4 days the clinical manifestations of the disease begin. They are characterized by sudden onset of high fever, cephalea,

myalgia, back pain, and arthralgia which is sometimes disabling. A cutaneous involvement occurs in 40–50% of the cases [82], and erythematous and pruriginous maculopapular rash can occur involving mainly the torso, besides facial edema. A vesicular-bullous edema can occur in children, with noticeable skin scaling related to petechiae and gingival bleeding. Hemorrhagic fever is uncommon but can occur. Contrary to dengue, the individual acquires permanent immunity after being infected by the virus.

Table 59.6 lists the main differential diagnoses of rashes in the adult population.

Table 59.6 Main differential diagnoses of rashes in adult population

Disease	Exanthem/related symptoms	Key characteristics/diagnosis
Pharmacodermias	Polymorphous exanthem often with presence of erythematous, confluent macules and papules that make up plaques Vesicles and blisters may occur The rash often begin on the torso and upper limbs Pruritus is a very common symptom. Low fever is also frequent	The rash usually occurs between the first and second weeks after drug use Always consider all medications being used by the patient, either the drugs of continuous and intermittent use Alertness signs for acute reactions: facial edema, peripheral hypereosinophilia, painful or grayish lesions, mucosal involvement
Contact dermatitis	Acute eczema: erythem, edema, papules, vesicles and even blisters Subacute eczema: exudation, crusts Chronic eczema: erythematous and lichenified plaques, scaling, and sometimes fissures	Focus on location – initially lesions occur in areas of allergen contact Pruritus and burning are usual symptoms Ask the patients about their occupation, hobbies, usual cosmetics, contact with plants and fruits, solar radiation
Pityriasis rosea	Multiple small lesions with 1–2 cm average, erythematous and scaling, oval lesions scattered on the torso, neck, and limb root Pruritus is a common symptom although of low intensity	Presence of a "mother patch" or "herald plaque": single oval or round erythematous scaling 2–10 cm plaque, displaying a typical peripheral scaling collarette on the outer margin On the torso, the lesions usually disseminate along the skin cleavage lines and display the typical appearance of "Christmas tree" pattern
Secondary syphilis	Roseoliform exanthem characterized by erythematous nonconfluent macules, with little or absence of pruritus, at first on the torso, periumbilical area and inner surface of limbs, rapidly disseminating to the rest of the body Generalized adenopathy is common. Fever, arthralgias, myalgias, alopecia, hoarseness, mucosal involvement may occur	The distinctive characteristic is the palmoplantar involvement with erythematous yellowish hardened and sometimes painful macules and papules Treponemal tests, such as the FTA-abs and the MHA-TP, and nontreponemal tests, such as the VDRL and the RPR, are positive for secondarism
Emerging dermatological viral diseases – dengue, Zika, chikungunya	Main transmission through the *Aedes* species insect bite Erythematous maculopapular exanthem prevailing on the torso and upper limbs. Face and neck may be sometimes involved Fever, malaise, myalgias, arthralgias, retro-orbital pain More common hemorrhagic phenomena in dengue	Rash is almost always found in Zika, very common in the chikungunya, and less common in dengue fever Origin or recent trips to endemic areas should raise suspicion PCR and serologies positive for the 3 viruses

Diagnosis

Because of the lack of specificity of most exanthems, their correct and precise diagnosis is often very difficult to make. When a diagnosis is not so obvious the physician must first characterize the rash according to the cutaneous primary lesions to limit the majority of the differential diagnoses. Flowchart 59.1 proposes a process of thought to make rash assessment easier.

After classification one must pay attention to lesion location, color (drug reactions tend to show a darker and more conspicuous color), presence of pruritus (it is generally present in most of pharmacodermias and absent in viral exanthems), pain (frequent in some pharmacodermias and KD), fever (related to infectious exanthems), lymphadenopathy (important in rubella and KD), diarrhea (common in exanthems caused by rotavirus and picornavirus), and the patient's general health condition (requiring prompt intervention when impaired). Also, the patient's history of contact with sick persons or recent travel (imported cases of diseases, such as measles and even rubella, are not uncommon) must be investigated.

Benign exanthems during childhood are often only clinically diagnosed, as is the case for hand-foot-mouth disease, infectious erythema, sudden exanthem, scarlatina, and varicella. Nevertheless, when in doubt about the diagnosis, specific tests are available most of the time, and when suspicious about any of those diseases additional tests must be carried out by the physician.

The diagnosis of measles, especially during outbreak periods, is usually easy. The Koplik spots are especially useful for diagnosis because, besides being pathognomonic, they are often present even before the exanthem. Since many countries have shown rare and sporadic cases of the disease, it is important for measles to be included in the differential diagnosis for all patients displaying fever and exanthem. According to the WHO, all patients displaying fever and macular-papular exanthem (not vesicular exanthem), related with cough, coryza, or conjunctivitis, must raise the suspicion of measles. Laboratory diagnosis can be made in different ways; the most used method being antibody detection of the immunoglobulin M (IgM) class against the measles virus in serum or oral mucosa secretions, usually positive for the early days of cutaneous eruption. Another diagnostic method is a four-fold or more increase in the virus-specific IgG titers. A single sample of positive IgG is not diagnostic, since it can simply represent a previous infection. Virus isolation through culture of nasopharyngeal, urinary, or

Flowchart 59.1   Diagnosis of rash in childhood
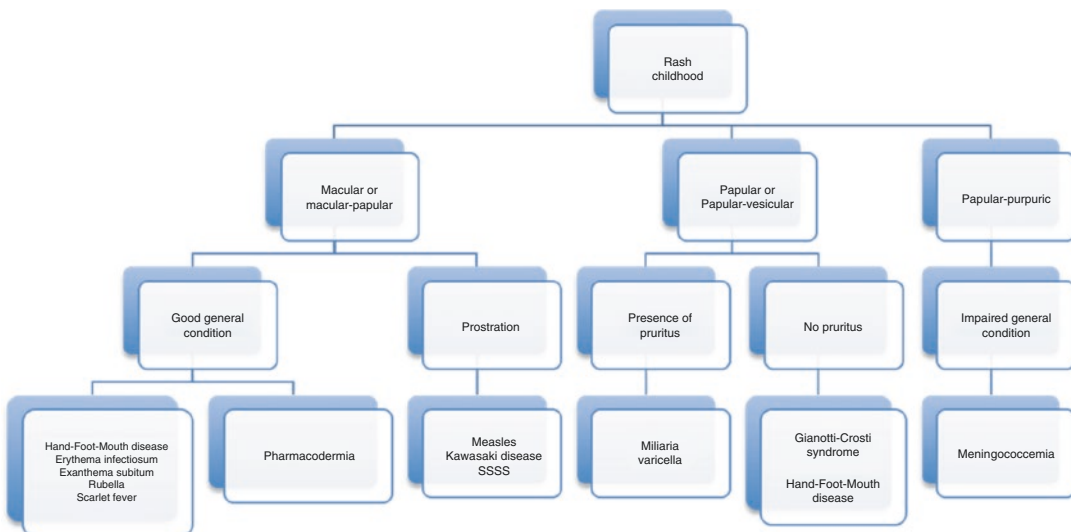
blood secretions, as well as magnification of the viral RNA through the polymerase chain reaction (PCR), can also be used, although they are more expensive and slower technologies [83].

The exanthem found in rubella is unspecific and common to other diseases, so laboratory tests are usually required. The gold-standard diagnostic method is viral RNA research in oropharyngeal and nasal secretions, urine, blood, or liquor using PCR, which can be positive up to a week before rash onset. However, serologic tests are more often used because of their widespread availability and low cost. Therefore, IgM and IgG antibody research are still very useful. IgM antibody positivity is commonly found from 4 to 30 days after disease onset, although it can be negative before the fifth day of rash development, with its repetition suggested after that period. A four-time increase in the IgG titers can be also considered diagnostic [33].

When meningococcemia is suspected diagnostic tests must be required, although they cannot postpone treatment implementation. Blood cultures must be collected before beginning antibiotic use, and hemodynamically stable patients may undergo lumbar puncture. With regard to cutaneous lesions, *Neisseria meningitidis* can be seen on Gram stain in up to 70% of cases. Latex agglutination tests using urine and liquor samples show low sensitivity despite their specificity. The PCR technique has been increasingly used because of its high sensitivity and specificity, despite not being widely used to date.

The SSSS diagnosis is based on clinical suspicion, although the *S. aureus* can be found and cultivated from skin, conjunctiva, nasopharynx, and pyogenic foci of feces. Skin biopsy sometimes can be useful to distinguish other disorders, and KD, TEN, primary sunburn, and extensive bullous impetigo are among the main differential diagnoses of the disorder. Table 59.7 lists the main diagnostic examinations for infectious diseases resulting in exanthem presentations.

GCS and miliaria are basically clinically diagnosed, and there are no specific diagnostic tests. However, in GCS attention must be paid to a history of systemic symptoms or recent infections as well as vaccination. Since the infectious agent spectrum related to GCS is affected by typically regional epidemiologic factors there is no universal

Table 59.7 Diagnostic laboratory tests when infectious diseases resulting in child rash are suspected

Disease	Diagnostic tests
Hand-foot-mouth disease	Oropharynx discharge, palmar-plantar lesions, and feces PCR
Exanthema subitum	IgM + / 4× increase of IgG levels against serum HHV-6 or HHV-7 Immunofluorescence, PCR blood mononuclear cells culture
Erythema infectiosum	Serum IgM + Parvovírus B19
Scarlet fever	Leukocytosis with prevalence of young and eosinophilic forms Antistreptolysin, antihyaluronidase, and antifibrolysin antibodies Oropharynx culture with growth of hemolytic Streptococcus β of group A
Rubella	Oropharynx and nasal secretions, urine, blood, and liquor PCR IgM + / a 4× increase in the IgG levels against the serum rubella virus
Measles	Discharge culture/PCR of the nasopharynx, urine, and blood IgM + / a 4× increase in the IgG levels against serum measles virus and the oral mucosa
Varicella	IgM + /a 4× increase in the IgG levels against the varicella zoster virus
Meningococcemia	Bacterioscopy and culture of cutaneous lesions, blood, and liquor Latex agglutination test
SSSS	Clinical diagnosis Pyogenic foci culture of skin, conjunctiva, nasopharynx, and feces

Table 59.8 Association between lesion location and probable cause of contact dermatitis

Location	Cause
Scalp	Hair coloring substances, shampoo, hair straightening products
Eyelids	Nail polish, make up products
Face	Cosmetics used on the face, hands, and hair
Ears	Earrings, perfume, shampoo
Lips	Lipstick, toothpaste, dyeing substances
Neck	Perfume, bijou
Armpits	Deodorants, fabrics
Genitals	Cosmetics, fabrics, condoms (latex)
Hands	Soaps, detergents, gloves, cosmetics, occupational exposure substances, plants
Feet	Shoes, socks, occupational exposure substances

recommendation regarding the pathogens to be investigated. In general, however, it is known that the Epstein–Barr virus, HHV-6, parvovírus B19, cytomegalovirus, A and B hepatitis viruses, syncytial respiratory virus, and rubella virus have already often been related to the disorder, as well as vaccines.

In drug eruption cases, the diagnosis is made through the clinical history, the patient's characteristics, and the physical examination. Laboratory tests help to assess the patient's systemic involvement, and the anatomopathologic test of the cutaneous injury, although unspecific, can help the diagnosis.

To diagnose ACD a deep anamnesis and clinical presentation are indispensable and often are sufficient to elucidate the dermatitis type and cause (Table 59.8). Patient evaluation must show possible exposures to substances in the patient's occupation, sports, and personal care; for children, the caregiver's history must be assessed. In ACD cases, the most effective method is the contact test or the epicutaneous test to confirm the etiologic diagnosis [63], indicated when this kind of contact dermatitis is suspected, and in all other cases of occupation-related contact dermatitis and chronic dermatitis not controlled by the most often used topical drugs [84]. The provocation test of use and the open test are other available

modalities, although they need to be used with caution.

Pityriasis rosea is a disease with an eminently clinical diagnosis because there is no specific laboratory test for this condition. However, the differential diagnosis is required with secondary syphilis at the secondary rash stage; therefore, a nontreponemal triage test, such as the Venereal Disease Research Laboratory test (VDRL), is indicated.

When facing a clinical suspicion of syphilis at any stage, laboratory investigation is mandatory. Serologic tests are divided into nontreponemal (VDRL and rapid test reagin (RPR)) and treponemal (fluorescent treponemal antibody absorption (FTA-abs) and microhemagglutination treponema pallidum test (MHA-TP)). The FTA-abs becomes positive 7–10 days after cancer onset, the MHA-TP after 10 days, and the VDRL after 15 days [73–75]. Hence, for secondary syphilis the nontreponemal tests are markedly positive, and should be confirmed through a treponemal test because of the various clinical situations that may yield a false-positive nontreponemal test (lupus, hanseniasis, hepatitis, pregnancy). Another noteworthy fact is that syphilis may increase the risk for HIV transmission; thus, HIV triage is strongly recommended for patients diagnosed with syphilis.

The emerging dermatologic viral disease diagnosis is made based on clinical and laboratory findings. Dengue fever, Zika, or chikungunya can be diagnosed through PCR research and the specific IgM and IgG serologic tests for each virus. In dengue cases when the occurrence of hemorrhagic disease is more common, the tourniquet test must be made: a 2.5-cm square (or an area around the thumb distal phalanx) is drawn, a blood pressure cuff is applied and inflated to the midpoint between the systolic and diastolic blood pressures for 5 min, then the number of petechiae that arise within the drawn square is count. The proof is considered positive when 20 or more petechiae are counted, and even in the negative cases a complete blood count is indicated.

Moreover, attention must be paid to changes in coagulation tests, platelet count, hematocrit, leukopenia, and hepatic enzymes. When Zika infection is suspected in a pregnant woman, the patient must be referred for possible fetal evaluation [80].

Therapeutic Approach

When facing an exanthem presentation, and after making a diagnostic hypothesis and possible differential diagnoses, the initial treatment of the patient is decided by the physician. Most exanthems are benign and self-limited, although some patients require careful monitoring and treatment, and even isolation and precautionary measures must be promptly initiated.

Viral exanthems, in general, do not require specific treatment; they only need support and symptomatic measures. Therefore, hand-foot-mouth disease, sudden exanthem, rubella, GCS, and miliaria generally require only symptomatic treatment.

Infectious erythema needs special treatment only for aplastic transient crisis, which involves supportive measures and blood transfusion, and for immunosuppressed patients. In these cases the use of standard human Ig is the treatment of choice besides immunosuppression correction.

For scarlatina cases the treatment of choice is penicillin, which can be started up to 8 days after presentation onset. Penicillin-allergic patients can receive erythromycin as well as macrolides [23].

For measles there is no effective antiviral therapy against the virus, but there is an indication for supplementary use of vitamin A. Thus, all measles-diagnosed children must receive 200,000 IU of vitamin A every 24 h for 2 days [28]. This was shown to be an effective measure to decrease the incidence of blindness and death, according to the WHO. In secondary bacterial infection cases mainly resulting in acute otitis media and pneumonia, antibiotic therapy must be initiated.

For varicella, immunocompromised children undergo symptomatic treatment, mainly antihistamines. However, antiretroviral therapy is indicated for specific cases when there is greater risk of disease aggravation. Acyclovir has been the preferred drug to treat varicella, but alternative drugs such as valacyclovir and famciclovir can be used. Acyclovir must be initiated preferably over the first 24 h for the following patients [26]:

- All patients older than 12 years old
- Patients with cutaneous or chronic pulmonary disorder
- Patients undergoing corticosteroid or long-term salicylate treatment

The usual acyclovir dose for children is 20 mg/kg, oral route, four times a day, not more than 800 mg/day, over 5 days. The adult dose is 800 mg/day, oral route, five times a day, over 5 days. Acute cases require intravenous acyclovir. Postexposure prophylaxis for the virus-exposed and immune-depressed patients under the same condition can be implemented through vaccination or use of immunoglobulin. Studies have shown that early vaccine use (up to 96 h post-exposure) is effective to prevent disease development and occurrence of its acute configurations. Intravenous human Ig (IVIG) must be used for the virus-nonimmune patients who cannot receive the vaccine and who are also at risk for developing acute varicella [26]. Therefore, intravenous human Ig is indicated for immunosuppressed patients, pregnant women, newborns whose mothers developed varicella 5 days before or 2 days after childbirth, and premature babies exposed to the varicella virus (specifically patients born with gestational age of 28 weeks or more whose mothers displayed no evidence of immunity against the virus, or patients of gestational age less than 28 weeks, and/or weighing less than 1,000 g).

Patients diagnosed with KD should receive IVIG at 2 g/kg, single infusion, for 10–12 h.

Related to the IVIG, acetylsalicylic acid must be started early at a dosage of 80–100 mg/kg/day, divided into four ingestions, and kept for at least 72 h following fever cessation (although some centers of excellence have kept a low dose for a long time) [38]. Studies recommend the use of corticosteroids (methylprednisolone pulse therapy) only for patients who had received two IVIG doses with no reaction whatsoever).

SSSS treatment depends on the extension and gravity of each case. Patients with confirmed disease and displaying good general condition can receive oral treatment against the *S. aureus*. β-lactamase-resistant antibiotics, such as cephalexin and flucloxacillin, given for at least 7 days [40, 41]. Also, the detached skin areas can be initially lubricated with mild moisturizer, and *S. aureus*-colonized patients must undergo topical antibiotic therapy. Acute patients must be taken to hospital, often in need of some time in the intensive therapy unit. The antibiotic of choice is intravenous oxacillin or vancomycin (mainly in areas showing a high rate of methicillin-resistant *S. aureus* or MRSA) [40, 41].

When meningococcemia is suspected, antibiotic therapy must be immediately initiated. Crystalline penicillin G is the antibiotic of choice, at 500,000 U/kg/day, divided into six doses. Cefotaxime 200 mg/kg/day, divided into three doses, or ceftriaxone 100 mg/kg/day, one or two doses, can be given [48]. Attention must be paid to individuals in contact with meningococcemia patients, since they must undergo appropriate chemoprophylaxis. Rifampicin, every 12 h, for 2 days, is indicated for children and adults. Single doses of ciprofloxacin and ceftriaxone can be also used for adults [48, 49].

The basic treatment of patients with a cutaneous drug eruption consists in symptom control and interruption of the drug responsible for the clinical presentation. After assessment of the used drugs, all of them must be discontinued. When the drug under suspicion is necessary for the patient, the potential risk/benefit has to be considered. In general, topical corticosteroids alleviate the pruritus and are often used in more circumscribed lesions. On the other hand, patients with acute forms of pharmacodermia usually need a systemic corticosteroid and even IVIG [54]. Hospital admission to improve monitoring is an indication for the acute and severe cases.

To treat contact dermatitis one must first try to identify the cause and, therefore, avoid repeat exposures. The adoption of protective measures, such as use of appropriate clothes, gloves, and barrier cream, is very helpful, and in some cases diet changes may be necessary, mainly in cases of nickel allergy; improvement can be seen when its ingestion is decreased [62]. In cases of acute eczema, wet packs soaked into 1/10 or 1/20 Burrow liquid or Alibour water can be used, and topical corticosteroids in gel, lotion, or cream may also be used. Extensive and acute cases can be treated with oral corticosteroids for a short time (usually 1 mg/kg/day over 3–14 days) [63]. For the chronic forms, topical corticosteroids as ointment are the usual choice; in some cases occlusive corticosteroids are used [84]. Calcineurin inhibitors, such as tacrolimus and pimecrolimus, are another option [85]. Oral antihistamines are useful for pruritus control only; when the lesions improve, treatments to recover the skin barrier are important.

In pityriasis rosea, the treatment in most cases involves patient education about the course of the disease and its self-limited character. Topical corticosteroids and, rarely, oral corticosteroids may be used in patients displaying extensive and pruritus-associated injuries. Phototherapy is another useful therapeutic procedure for disease control [86]. In recent years, studies have used systemic erythromycin, azithromycin, and acyclovir [87, 88], given that there may be evidence for acyclovir to have some benefit in disease control.

All syphilis cases, regardless of form, have penicillin as the drug of choice. In the early forms, benzathine benzylpenicillin, 2.4 million

IU by intramuscular injection, at a single session is recommended. There are protocols that associate a second dose 1 week later in secondary syphilis and early latent syphilis. For patients with tardive forms, three doses of penicillin benzathine are indicated: benzathine benzylpenicillin, 2.4 million IU also by intramuscular injection, once weekly for three consecutive weeks (Table 59.5). The alternative for allergic patients involves the use of tetracycline or doxycycline, although it is important to underscore that HIV-positive patients or pregnant women have an indication of desensitization to use the first-choice drug [75, 76, 89, 90]. Serologic post-treatment follow-up is conducted with nontreponemal tests, since treponemal tests remain positive regardless of treatment, and it is expected for the early forms to show a decrease of at least two titrations from the starting value up to 6 months after treatment has ended.

There is no specific treatment for dengue, Zika, and chikungunya. All patients must go through powerful rehydration therapy and be given symptomatic drugs with no acetylsalicylic acid. Signs of acute hemorrhagic disease and shock demand hospital admission and eventually intensive care [78].

Future Perspectives

The advance of technology and the body of knowledge in recent years concerning many diseases has yielded a significant increase of diagnostic accuracy in the cases of rash. Many laboratory tests nowadays, either serologic or viral load detection tests, are available in many healthcare clinics around the world. There is an increased ability to determine the cause of a rash and approach it the best possible way.

Many diseases already controlled and even eradicated in some parts of the world have now once again become part of the differential diagnoses of exanthem following recent outbreaks in both underdeveloped and developed countries, such as the case of measles. This reasserts the need for constant alertness and massive immunization for the appropriate control of many infectious diseases. In addition, the emerging dermatologic viral diseases have become a major world concern because of their high morbidity rate, with dengue fever, Zika, and chikungunya among their number.

Besides the infectious causes, pharmacodermias are still, and will continue to be an important cause of rash in the adult and pediatric population. Every year new drugs are developed, mainly chemotherapeutic, antihipertensive, and antimicrobial, and the physician must be fully aware of the possible adverse effects of such new drugs. Moreover, since health care systems are being perfected, more patients have had access to medical assistance and consequently to these drugs, which makes the possible occurrence of pharmacodermias even more important.

Thus, the knowledge and the correct management of the main causes of rash are increasingly more significant and necessary, given that cases of rash will probably continue to happen for many different reasons.

Glossary

Biett's collarette A syphilitic symptom characterized by a thin white ring of scales on the surface of a macule or papule.

Filatov sign A typical sign of scarlet fever characterized by paleness around the mouth and congestion of the cheeks.

Koplik spots Spots characterized by clustered, small, white lesions on the buccal mucosa (opposite the upper first and second molars), pathognomonic for measles. The spots resemble tiny grains of white sand, each surrounded by a red ring.

Papular-purpuric gloves and socks syndrome An acute dermatosis characterized by a papular-purpuric edematous rash in a distinct "gloves and socks" distribution often accompanied by fever, asthenia, and lymphadenopathies. It is mainly caused by parvovirus B19 (B19V) although other viruses and drugs may be involved.

Pastia's lines A clinical sign whereby pink or red lines formed of confluent petechiae occur in areas of skin creases, such as the axilla, the

neck, the antecubital fossa, and the popliteal fossa. This is a typical sign of scarlet fever.

Primary skin lesions Blister: Raised lesion, more than 1 cm wide, with internal liquid content.Macula: Flat nonpalpable lesions, less than 1 cm wide, showing inconspicuous texture and/or color change.Nodule: Palpable raised and indurated lesion usually deeper than the papule.Patch: Flat nonpalpable lesion, more than 1 cm wide, showing discrete texture and/or color change.Papule: Circumscribed palpable lesion, above skin surface, less than 1 cm wide.Plaque: Palpable and raised lesion, above skin surface, more than 1 cm wide.Pustule: Raised surface lesion with internal yellow content (pus).Vesicle: Raised lesion, less than 1 cm wide, with internal light liquid content.

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Suggested Literature

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Pigmented Lesions

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Introduction

Pigmented moles and nevi are the most common neoplasms found in humans [1]. The incidence of melanocytic nevi in newborns is slightly more than 1% [2]. The incidence increases in infancy and adulthood, with a peak at puberty and adolescence. The size and pigmentation of these lesions also increase during adolescence, pregnancy, or after estrogen and corticosteroid therapy. Between the second and third decades of life, most Caucasians acquire their maximum number of lesions, and later in life most lesions tend to fade and eventually disappear.

Skin tumors can be differentiated into several groups: epidermal surface; epidermal appendages; fibrous, neural, vascular, fatty, muscular, and osseous tissues; melanocytic; and malignant. The term *nevus* refers to a circumscribed congenital abnormality of any type present at birth. When this term is used, it is important to include a qualifying adjective (epidermal, melanocytic, pigmented, vascular) to specify the particular cell of origin. Being in common use this term is also used in a loose manner to refer to a benign tumor of pigmented cells [1].

In contrast, moles are pigmented cutaneous lesions not present at birth that are apparently hereditarily predetermined. In general, moles appear during childhood and adolescence and are flat or slightly elevated. In adulthood they tend to be polypoid or dome-shaped, sessile, or papillomatous [1].

Pigmented lesions may comprise melanocytes or nevus cells. Both are of neural origin. A melanocyte is a dendritic cell that produces melanin and transfers it to the keratinocytes and hair cells, supplying the pigment to skin and hair. It originates in the neural crest and early in fetal life it migrates with the nerves to the skin. Many types of skin lesions may appear because of the melanocytic cells remaining in the dermis after birth, such as Mongolian spots, blue nevi, and the nevi of Ota and Ito [1].

Theories suggest that nevus cells arise from a bipotential precursor cell that develops into a melanoblastic or schwannian nevoblast. In this theory, the nevoblasts develop into epidermal nevus cells that give rise to the junctional and compound nevi. In addition, the schwannian nevoblasts develop into neural nevi cells and intradermal nevi [3]. In the most popular theory, nevus cells have a dual derivation and develop from the melanocytes in the epidermis and Schwann cells of the neural sheath [4]. A line of Schwann cells in the peripheral nerves appear to form a pathway between the central nervous

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system and the skin. These cells migrate to the dermis and give rise to a number of dermal tumors. Nevus cells, therefore, may locate at the dermal–epidermal junction (junction nevi), within the dermis (intradermal nevi), or be a combination of both (compound nevi) [1].

In the clinical evaluation the most important step is to differentiate the pigmented lesions from others. Using this approach it is often difficult to establish the melanocytic origin. Lesions such as basocellular carcinoma or seborrheic keratosis sometimes require better knowledge about other methods of evaluation, such as dermoscopy and pathology. Although dermoscopy and confocal microscopy are discussed in detail in a specific chapter elsewhere in this book, the description of lesions in this chapter some mentions details about these instruments. Some structures described in dermoscopy, such as aggregated globules, typical pigmented network, pseudonetwork, branched streaks, and parallel pattern, are the most important features for the diagnosis of benign melanocytic lesions [5]. Pathology is the gold-standard method of diagnosis to differentiate melanocytic from non-melanocytic lesions, and anatomopathologic characteristics for each lesion will be described. The use of immunohistochemistry as a complementary method of diagnosis can improve this evaluation.

Nevocellular or Common Pigmented Nevi

Concepts Nevocellular or pigmented nevi are lesions comprising nevus cells. Based on the location of the nevus cells, they are subdivided and described as junctional, intradermal, or compound lesions. Intradermal moles and nevi only have nests cells in the dermis. In junctional nevi, nevus cell nests are confined to the dermal–epidermal junction, and compound nevi have nevus cells nests in both locations.

Clinical Presentation and Diagnosis Pigmented nevi have a wide range of clinical appearances and locations. The prevalence varies with age, race, and perhaps genetic and environmental factors. Few nevi are present at birth or childhood;

they progressively increase in number, reaching a peak at the third and fourth decades of life, and then disappear with age. The most important factors related to number, development, and growth of nevi are skin color, race, genetic and familial occurrence, sun exposure, systemic immunosuppression, pregnancy, and hormonal diseases [6].

Pigmented nevi are usually well circumscribed, round or ovoid, regular and symmetric with a size ranging between 2 and 6 mm. They may occur anywhere on the skin surface (Fig. 60.1) and vary from flat to slightly elevated or dome shaped, nodular, verrucous, polypoid, or papillomatous. Junctional nevi are commonly hairless macules with color ranging from light to dark brown or brownish black. Most of them are circular, elliptical, or oval with few variations in colors and shapes. They are more common in children and located on palms, soles, and genitalia [1]. Compound nevi are more common in older children and adults, tend to be elevated with shades of brown, and may have coarse hairs within the lesion. In adolescence they frequently tend to increase in thickness and pigmentation. Intradermal nevi are seen most frequently in adults after the third decade of life and tend to fade with maturation, when nevus cells are often destroyed and replaced by fibrous or fatty tissue. They are
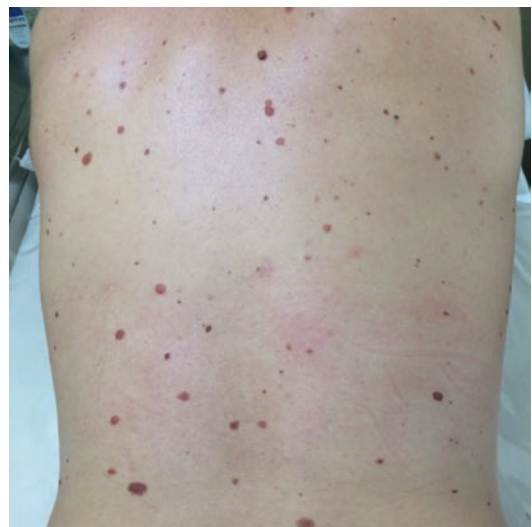
Fig. 60.1 Melanocytic nevi

usually dome shaped, sessile, or pedunculated and range in size from a few millimeters to 1 cm or more. The color varies from nonpigmented to brown or black [1].

Depending of the characteristics of the nevi, sometimes it may be very difficult to distinguish them from other lesions such as seborrheic keratosis, dermatofibromas, and neurofibromas. The most important differential diagnoses are dysplastic nevi and melanoma. Common nevi usually appear to be smaller and show clinical characteristics such as symmetry, regularity in shape, and well-defined borders. Furthermore, colors such as red, blue, gray, and black are more common in dysplastic nevi and melanomas.

Congenital Melanocytic Nevi

Concepts Congenital melanocytic nevi are moles present at birth. They consist of intraepidermal, dermal, or both benign melanocytic proliferations with a wide range of sizes, locations, and clinical appearances. Although it has been suggested that the increased incidence of malignant melanoma in large nevi may be related to the increased number of cells, studies suggest that small congenital nevi also have an increased risk of malignant degeneration [7]. Small congenital nevi (less than 1.5 cm in diameter), occur in 1% of all newborns and have an estimated lifetime risk of developing melanoma of 2.6–4.9% [8]. The risk of developing melanoma in medium-sized congenital nevi (measuring 1.5–20 cm in diameter) is uncertain; and large or giant congenital pigmented nevi, measuring greater than 20 cm in diameter, are believed to have 6.3% lifetime risk for developing malignant melanoma [7, 9].

Clinical Presentation and Diagnosis Small and medium-sized congenital nevi usually are oval or round, flat, pale tan to light brown macules or papules. Others are well-circumscribed lesions with mottled freckling. With time they become elevated, and coarse dark brown hairs may or not become prominent. Giant nevi frequently lie in the distribution of a dermatome

Fig. 60.2 Giant melanocytic nevi in arm and hand

and vary in size. Furthermore, they may cover limbs or extensive areas of trunk (Fig. 60.2). Their color ranges from dark brown to black and over 95% have a hairy component consisting of large coarse terminal hairs [1]. It is common to also observe a verrucous or papillomatous surface and an irregular margin. Almost invariably satellite nevi appear at the periphery of the lesion, and numerous other pigmented nevi coexist elsewhere on the body. Giant hairy nevi, particularly those on the scalp and neck, may be associated with leptomeningeal melanocytosis and neurologic disorders such as epilepsy or other focal neurologic abnormalities. Those that overlie the vertebral column may be associated with spina bifida or meningomyelocele [1].

Characteristically dermoscopy demonstrates a target network, focal thickening of network lines, target globules, skin furrow hypopigmentation, focal hypopigmentation, hair follicles, perifollicular hypopigmentation, vessels, and target vessels.

Halo Nevus

Concepts and Clinical Presentation Halo nevus (Sutton's nevus or leukoderma acquisitum centrifugum) consists of a single or multiple pigmented skin lesion centrally placed surrounded by a 1- to 5-mm halo of depigmentation (Fig. 60.3). This common disorder occurs between 3 and 45 years of age, usually with onset in late adolescence [1]. Compound and intradermal nevi are the most frequently

Fig. 60.3 Halo nevi

associated melanocytic lesions. However, it may also occur with blue nevi, neuromas, neurofibromas, melanomas, metastatic lesions, seborrheic keratoses, angiomas, molluscum contagiosum, warts, basal cell carcinoma, and congenital nevi. The cause appears to be related to an immunologic destruction of melanocytes and nevus cells. About 30% of patients with halo nevi have a tendency to vitiligo. It may occur on almost any cutaneous surface and is usually asymptomatic. The natural course tends to a spontaneous resolution and disappearance of the central lesion. Later, complete resolution leads to repigmentation of the site [1].

Diagnosis Dermoscopy reveals in the center of these lesions usually a regular pigmented network, dots and globules, an amorphous area, or a pseudonetwork pattern when lesions are located on the face. During involution, these structures disappear. The histologic examination reveals reduction or absence of melanin and dense inflammatory infiltrate around the central lesion.

Therapeutic Approach The prognosis for benign lesions is excellent, but attention must be directed to the rare cases in which a malignant melanoma or metastatic lesions of this tumor

may be the affected lesion [1]. The correct management consists in the clinical and the dermatoscopic observation of central lesion. With benign characteristics (color, regularity, shape, development) and its permanence over the consultations, the lesion may be observed until it has resolved. Lesions with unusual appearance and evolution require surgical excision of the central tumor and its surrounding halo [1].

Nevus Spilus

Concepts and Clinical Presentation Nevus spilus (speckled lentiginous nevus, zosteriform lentiginous nevus) is a solitary, flat, brown patch dotted by smaller dark brown to blackish brown freckle-like areas of pigmentation ranging from 1 to 6 mm of diameter (Fig. 60.4). These dots vary from junctional and compound nevi to Spitz and blue nevi. Nevus spilus may vary from 1 to 20 cm in diameter and appear on any area of the face, trunk, or extremities without relation to sun exposure. Larger lesions may be unilateral or segmental, or follow Blaschko lines affecting substantial parts of the skin (a limb, trunk). It is a common disorder, usually presenting at birth, although it may appear at any age and persists indefinitely. Males and females are equally affected. Nevus spilus should be considered with the same potential for neoplastic change as any other pigmented nevus.

Diagnosis The dermoscopy presents a thin and bright reticular background and outbreaks with pigmented network and aggregated globules.

Therapeutic Approach There are reports about dysplastic transformation or melanomas appearing from these lesions. For this reason, periodic clinical and photographic observation is recommended. In addition, biopsy and surgical excision is necessary for lesions with typical dysplasia or a clearly documented onset [10].

Fig. 60.4 Nevus spilus

Fig. 60.5 Becker's nevus on the back

Becker's Nevus

Concepts Becker's nevus (pigmented hairy nevus or nevus spilus tardus) may begin in childhood or shortly after puberty. It is six times more common in males than in females and may occur in all races [11]. The pathogenesis is unclear, but the clinical features seen in individuals with this disorder suggest a localized increase in androgen sensitivity. Furthermore, a familial occurrence seen in some patients demonstrates a genetic influence [12]. The association with other abnormalities (such as unilateral breast, areolar hypoplasia, pectus carinatum, spina bifida) suggests an organoid nevus, as a part of the spectrum of epidermal nevi and the epidermal nevus syndrome [13]. There are no nevus cells and no increases in the number of melanocytes; therefore, malignant transformation does not occur.

Clinical Presentation and Diagnosis Becker's nevus is a relatively frequent and asymptomatic disorder. Usually it begins as a grayish brown pigmentation, unilateral on the chest, back, or upper arm, that spreads in an irregular format until it reaches an area 10–15 cm in diameter (Fig. 60.5), often surrounded by islands of blotchy pigmentation. It has been reported on other areas of the trunk, face, neck wrist, buttocks, and shins. After 1–2 years coarse hairs appear in the region. The hairy area does not necessarily coincide with the pigmented area. The hyperpigmentation and hypertrichosis tend to persist for life. Acneiform lesions have been described in association with Becker's nevus.

Histopathologic features reveal epidermal thickening, elongation of the rete ridges, and hyperpigmentation of the basal layer. Network, focal hypopigmentation, skin furrow hypopigmentation, hair follicles, perifollicular hypopigmentation, and vessels are the main dermoscopic features. Differential diagnosis includes congenital melanocytic nevus, plexiform neurofibroma, and smooth muscle hamartoma.

Therapeutic Approach The treatment of this disorder is purely cosmetic (electrolysis, depilation, camouflage), and therapy with lasers have also been described (Q-switched, Nd:YAG) [14].

Freckles

Concepts, Clinical Presentation, and Diagnosis Freckles (ephelides) are red or light brown circumscribed macules, round, oval, or irregular, usually less than 5 mm in diameter. These lesions appear in early childhood, generally between 2 and 4 years of age, especially on sun-exposed areas of the skin (face, shoulders, upper back), and tend to fade during the winter and in adult life (Fig. 60.6) [1]. It appears to be inherited as an autosomal dominant trait linked with a tendency to fair skin and red or reddish-brown hair. There is seasonal variation in their appearance. They become darker and more confluent during the summer and are smaller and lighter during the winter [1]. The sun increases the melanogenesis and the transport of melanosomes to keratinocytes. Freckles do not have tendency to malignant transformation.

Histopathologic features include increased melanin pigmentation of the basal layer without an increase in the number of melanocytes, which are more arborized and reactive to dopa than adjacent skin and also contain more melanosomes [1].

Therapeutic Approach The treatment is based on avoidance of sun exposure and covering makeup. Sunscreens permit a more uniform tan whereby freckling is less pronounced. Peeling, cryotherapy, and hydroquinone use may be partially effective. Laser therapy also is effective.

Fig. 60.6 Freckles

Lentigines

Lentigines are seen in all races and equally in both sexes. They are small, tan, dark brown or black, flat, oval, or circular lesions. They usually begin in childhood and may increase in number during adult life. They vary from 1 to 5 mm in diameter and may occur on any cutaneous surface or, occasionally, on the mucous membrane or conjunctiva of the eyes. The pigmentation is uniform and darker than that seen in ephelides, and the color is unaffected by sun exposure [1]. They may occur as a single lesion or be multiple. Generalized or multiple lentigines can be an isolated phenomenon with no disease involved, present at birth or later in childhood or adult life. However, lentigines may be seen genetic diseases with other multiple clinical manifestations, such as leopard syndrome, Peutz–Jeghers syndrome.

In mucous membranes lentigines often have nonhomogeneous irregular borders, with areas lacking pigmentation and varying in size and number. These lesions may grow slowly during months or years and also present with or without variations in pigmentation.

Solar Lentigines (Senile Lentigines, Liver Spots)

Concepts and Clinical Presentation Solar lentigines are multiple light or dark brown macules related to solar explosion. They usually appear in the Caucasian population older than 60 years and are located on the forearms, face, chest, neck, and dorsal area of the hands (Fig. 60.7). However, they may also be observed in younger adults with heavy solar exposure. The shape of these lesions is well circumscribed or confluent, oval to round, varying from 3 mm to 2 cm in diameter. They may slowly disappear with sun protection. Solar lentigines are an independent risk factor for the development of melanoma.

Diagnosis For the evaluation of these lesions it may be necessary to use Wood's lamp, dermoscopy, and histopathologic examination. Differential diagnosis includes junctional and compound melanocytic nevi, ephelides, actinic

Fig. 60.7 Solar lentigines

keratosis, pigmented actinic keratosis, seborrheic keratosis, hemangioma, cutaneous hemorrhage, and cutaneous melanoma.

Dermoscopy demonstrates a faint pigmented network, fingerprint structures, or uniform pigmentation.

Histopathologic features include an increase in the number of melanocytes just above the basal layer, and an increase of melanization of the keratinocytes of the basal layer. The etiology is unknown but seems to be related to genetic modifications of the neural crest.

Therapeutic Approach Treatment other than for cosmetic purposes is ordinarily not indicated. For senile lentigines, it is important to monitor for melanoma or nonmelanoma cutaneous cancer. Clarifying agents are not effective, although cryotherapy and laser surgery may help. Prevention with sun protection is necessary [1, 6].

Café-au-Lait Spots

Concepts, Clinical Presentation, and Diagnosis Café-au-lait spots are large flat lesions, round or oval, of light brown to dark brown pigmentation, found in 10–20% of normal individuals. They may occur anywhere on the skin and are frequently present at birth. In addition, they may be unique or multiple, often increasing in number and size with age. They vary from 1.5 cm or less to 15–20 cm in diameter (Fig. 60.8). The average size varies from 2 to 5 cm in adults. These macules may be a sign of neurofibromatosis and may be associated with other neurocutaneous disease, for example McCune–Albright

Fig. 60.8 Café-au-lait spot on the back

syndrome. There is no risk of malignancy. Multiple lesions are rare in the normal population and should alert the physician to the possibility of an associated disease [1].

Café-au-lait spots occur in 90% of patients with neurofibromatosis. Characteristically, six or more lesions greater than 1.5 cm in diameter may be observed in this disease. Smaller spots in the axilla, called axillary freckling, may also serve as a valuable diagnostic sign of neurofibromatosis (Crowe's sign). In addition there is an increased incidence of café-au-lait spots in patients with tuberous sclerosis, epidermal nevus syndrome, Bloom's syndrome, Sylver's syndrome, basal cell nevus syndrome, Gaucher's disease, ataxia-telangiectasia, and Turner's syndrome [6].

Histopathologic examination reveals an increase in pigment in the basal layer of the epidermis. Ultrastructural examination may reveal giant pigmented granules in the keratinocytes and melanocytes, particularly in those of individuals with neurofibromatosis [1]. The number of melanocytes per unit area in patients with neurofibromatosis may be increased, decreased, or equal to that in normal-appearing surrounding skin [15]. Differential diagnosis includes nevus spilus, Becker's melanosis, mastocytoma, postinflammatory hyperpigmentation, acquired melanocytic nevus, congenital nevus, and lentigines.

Therapeutic Approach Treatment is unnecessary [1]. The results with hydroquinone and laser therapy are poor with a high risk of hyperpigmentation. Camouflage can help for cosmetic appearance.

Dermal Melanocytic Lesions

Mongolian Spots

Concepts, Clinical Presentation, and Diagnosis Mongolian spots are flat dark brown to gray or blue-black large macular lesions, poorly circumscribed and reaching more than 20 cm. They may present as a single or multiple lesions, usually located over the lumbosacral area, buttocks, lower limbs, and shoulders of normal infants (Fig. 60.9). It may be seen in all races, especially in blacks, Asians, Indians, Hispanics, and less frequently in Caucasians (9.8%) [1]. The spots develop in utero, present at birth, in both sexes, and often fade during the first 1 or 2 years of life [1]. Occasionally they persists into adulthood, although these lesions usually disappear by 7–13 years of age [16].

The color seen is a result of the presence of melanocytes located deep in the dermis, probably as a result of an arrest during their embryonic migration from neural crest to the epidermis where they suffer cellular death. The blue color depends on the Tyndall effect (a phenomenon whereby light passing through skin is scattered as it strikes particles of melanin). Colors of shorter wavelengths (blue, indigo, and violet) are scattered to the side and backward to the skin surface, thus creating the blue-black or slate-gray discoloration [1].

Clinical morphology aids the differential diagnosis with nevus of Ota and nevus de Ito, maculous blue nevus, trauma, and hemangiomas. When in doubt, the diagnosis may be confirmed by histopathologic examination of lesions. Histopathology shows the presence of collections of elongated, slender, spindle-shaped, dopa-positive melanocytes that run in parallel to the skin surface, deep within the dermis or around the cutaneous appendages.

Therapeutic Approach Treatment is unnecessary. Cosmetic camouflage and laser therapy may help [1, 6].

Nevus of Ota

Concepts, Clinical Presentation, and Diagnosis Nevus of Ota (nevus fuscoceruleus ophthalmomaxillaris) represents a bluish gray discoloration of the skin of the face, usually unilateral. Size and shape may vary (round, oval, serrated) and the lesion is located on the skin supplied by the first and second divisions of the trigeminal nerve, especially the periorbital region, the forehead, nose, malar area, and temple (Fig. 60.10). In 5–15% of patients nevus of Ota may be bilateral,

Fig. 60.9 Mongolian spot

Fig. 60.10 Nevus of Ota

and in many cases the lips, palate, pharynx, eardrum, and nasal mucosa are involved. About two-thirds of patients have a patchy bluish discoloration of the sclera of the ipsilateral eye, occasionally also affecting the conjunctiva, cornea, retina, iris, and optic nerve. It may grow with time and generally persists throughout life (although some have been observed to fade over the course of years). Malignant transformation and sensorineural deafness are rare [1].

Approximately 50% of lesions are congenital; the remainder appear during the second decade (puberty) or are associated with pregnancy. Most commonly seen in Asians and blacks, it has been described also in Caucasians. It is more commonly seen in females (80% occur in females) [1].

The characteristic color is due to the production of melanin from dendritic and elongated melanocytes located in dermis, especially in the upper-third portion, scattered among the collagen bundles.

Considering the colors, shapes, and histopathologic features, the nevus of Ito (nevus fuscoceruleus acromiodeltoideus), differs from nevus of Ota by its location. It tends to involve the shoulder, supraclavicular areas, sides of the neck, and the upper arm, scapular, and deltoid regions. It may occur alone or be seen in conjunction with the nevus of Ota.

Mongolian spots, blue nevus, facial melasma, nevus spilus, and vascular malformations are part of differential diagnosis.

Therapeutic Approach Monitoring of glaucoma and ocular melanoma by the ophthalmologist is important. Cosmetic camouflage is necessary in many cases. Successful treatment has been obtained with laser ablation by Q-switched ruby, alexandrite, and Nd:YAG lasers [17, 20].

Blue Nevi

Concepts, Clinical Presentation, and Diagnosis Blue nevi (blue nevi of Jadassohn–Tièche) usually are acquired in childhood and adolescence, although 25% appear in adult life. They are benign tumors constituted by dermal melanocytes. These lesions represent hamartomas

Fig. 60.11 Blue nevi in arm

that result from the arrested embryonal migration of melanocytes limited to the dermal–epidermal junction. Their color is the result of the Tyndall phenomenon. Blue nevi may be divided in two groups: common and cellular.

Common blue nevi are small, round or oval, dark blue or bluish black, smooth-surfaced and sharply circumscribed lesions (Fig. 60.11). In addition, they may be a slightly elevated dome-shaped nodule or plaque ranging from 2 to 10 mm in diameter. Usually isolated, they may occur on any part of the body. Areas of predilection include the buttocks, dorsal aspect of the hands and feet, scalp, and extensor surfaces of the forearms. Blue nevi usually remain unchanged and persist throughout life. Malignant degeneration of this type is rare. Dermoscopy of common blue nevi is characterized for its grayish blue or blackened blue homogeneous pigmentation [1].

Histopathologic examination reveals compactly arranged and elongated spindle-shaped, flattened, or fusiform melanocytes grouped in irregular bundles, mainly in the middle and lower third of the dermis. These cells have long dendritic processes, with their long axes parallel to the epidermis. Occasionally the melanocytes may extend to subcutaneous layer or epidermis. The amount of collagen is usually increased, giving a fibrous appearance [6].

Cellular blue nevi are less common and larger than common blue nevi, generally measuring more than 1 cm in diameter. They present as blue or grayish blue, smooth-surfaced nodules or plaques occasionally with an irregular surface. Cellular blue nevi appear in a relatively high

incidence over the buttocks, sacrococcygeal areas, and dorsal aspect of hands and feet, although common blue nevi are five times more common. There is a low risk of malignant transformation, which should be suspected if the following features are observed: sudden increase in size with multinodular appearance, asymmetry, infiltrative changes, and ulceration. They are locally aggressive, more common on the scalp, and in about 5% may present with the risk of producing regional lymph node metastases. Except for the local involvement, patients may be asymptomatic for many years after the primary tumor excision [1].

Histopathology reveals nodular islands composed of densely packed, large, rounded, or spindle-shaped cells with variously shaped nuclei and abundant pale cytoplasm. Round islands of these melanocytes are often seen in the subcutaneous layer and may appear atypical with nuclear pleomorphism.

Traumatic tattoos, vascular lesions, primary melanoma and its metastasis, atypical nevi, dermatofibroma, pigmented basal cell carcinoma, apocrine hidrocystoma, nevi of Ota, hamartomas, and spindle cell nevus are part of the differential diagnosis of blue nevi.

Therapeutic Approach The treatment for lesions of less than 1 cm diameter is conservative. Larger lesions with atypical characteristics, a multinodular or patch aspect, asymmetry, or undergoing any transformation should be considered for histopathologic examination. Many authors consider the treatment of choice for both types of blue nevus to be conservative surgical excision with careful histologic examination. Patients who have cellular blue nevi should be examined for the presence of regional lymphadenopathy [1].

Pigmented Lesions Important in the Differential Diagnosis of Melanoma (See Also Chap. 14)

Spitz Nevus

Concepts, Clinical Presentation, and Diagnosis Spitz nevus (spindle cell nevus, spindle and epithelioid nevus) is a benign lesion of melanocytic origin that can occur anywhere on the cutaneous surface, more often on the face, usually the cheek of children and adolescents. It is believed that about 1% of lesions surgically removed from children exhibited histologic characteristics of Spitz nevus, in any age group and in both sexes. These lesions have certain histologic features that may resemble malignant melanoma and may be a cause of concern to physicians and pathologists [18]. No etiologic factors have been identified, but eruptive cases have been identified in immunosuppressed patients and pregnancy.

Clinically the lesions present as a smooth-surfaced, hairless, dome-shaped papule or nodule with a distinctive reddish brown color, usually single or less often multiple. Spitz nevi may vary in size from a few millimeters to several centimeters, usually ranging from 0.6 to 1 cm in diameter (Fig. 60.12). In some lesions, particularly those on the extremities, the reddish color is replaced by a mottled brown to tan or black appearance, often with a verrucous surface and an irregular margin [1]. Multiple or disseminated cases may be seen with hundreds of lesions of sudden onset, on any part of the body, with the exception of palms, soles, and mucous membranes. These cases tend to be polymorphic, more often in adults, with a possibility of spontaneous regression and no reported cases of malign transformation [1].

Atypical cases have one or more characteristics that differ from conventional lesions, such as larger size, asymmetry, ulceration, pagetoid

Fig. 60.12 Spitz nevus

dissemination, or high density of melanocytes in dermis.

The histologic pattern of this disorder appears to be a variant of the compound nevus. The nevus cells are pleomorphic and generally consist of spindle-shaped and, less frequently, polygon-shaped epithelioid cells. Multinucleated giant cells and mitotic figures complete the histopathologic features. This benign tumor can be differentiated from malignant melanoma by the presence of spindle and giant cells, and absence or sparseness of melanin, edema, and telangiectasia of the stroma and increased maturation of the tumor cells in the deeper aspect of the dermis. Important characteristics that aid the diagnosis are recognition that the cells are larger than those of common melanocytic nevi and the coalescent eosinophilic globules resembling colloid bodies (Kamino bodies), which are present in the basal layer above the tips of dermal papillae [1, 19, 20].

The differential diagnosis includes intradermal nevi, pyogenic granulomas, juvenile xanthogranulomas, hemangiomas, adnexal tumors, dermatofibromas, mastocytomas, and malignant melanomas.

Therapeutic Approach There is controversy regarding the management of these lesions. Some authors take a conservative approach, because the histopathologic appearance of incompletely removed lesions or biopsied lesions that leave a slight residual cellular or vascular component may be misinterpreted as malignant melanoma. Total conservative surgical excision is frequently recommended. In addition, other authors recommend removal with at least 1 cm of margin for atypical lesions and a periodic evaluation every 6 or 12 months.

Reed Tumor

Concepts, Clinical Presentation, and Diagnosis Reed tumor represents a pigmented form of Spitz nevus. They are less common than Spitz nevi and are seen especially in women of a mean age of 25 years. These lesions present with a mottled brown to tan or black appearance and

Fig. 60.13 Reed tumor

are uniform in color, often with a verrucous surface and irregular margin (this lesion may easily be confused with a malignant melanoma). In addition, Reed tumors may be flat or slightly elevated in shape, usually measuring an average of 4 mm (variation at 1.5–10 mm), particularly on the extremities. Dermoscopy often demonstrates a dark central area without structures, with globules or pseudopodia on the periphery, symmetrically arranged (Fig. 60.13). Variations in this pattern are seen in atypical cases [1, 6].

The differential diagnosis includes melanoma, atypical nevus, blue nevus, angiokeratoma, and pigmented basal cell carcinoma.

The principal histologic characteristics are ribbons of thin and uniform fusiform cells closely organized with granular melanin and streaky tissue slits. The nuclear appearance is homogeneous with subdued chromatin. The histopathologic examination is essential for the correct diagnosis [1, 6].

Therapeutic Approach The natural evolution is unknown. The knowledge about the association of atypical variants with melanoma is evidence of this rare transformation. The recommended treatment is total surgical excision with free margins to avoid recurrence. The pathologic characteristics of Reed tumor are extremely difficult to distinguish from melanoma. When atypical characteristics are seen, surgical excision is recommended with margins between 5 and 10 mm and medical monitoring for 6 or 12 months [1, 6].

Recurrent Nevus

Concepts and Clinical Presentation A recurrent or a persistent nevus is the development of a melanocytic lesion where a previous benign nevus was removed [21]. Many times it may clinically, dermoscopically, and histologically resemble melanoma, for which reason it has been called "pseudomelanoma." However, many authors find this term confusing and misleading, since recurrent nevi are benign and should not be mistaken for recurrent melanomas.

Recurrent nevi occur after incomplete removal of a melanocytic nevus. It may be observed after shave biopsies, electrocoagulation, or laser therapy [21]. The occurrence of this phenomenon can be explained by the reminiscent melanocytes in the adnexal structures, which migrate into the regenerating epithelium [22, 23]. During the healing process and scar formation, these melanocytes may be stimulated to proliferate [21].

Clinically, recurrent nevi are characterized by dark brown to black pigment in the scar, often exhibiting bizarre forms [21, 24]. Lesions may also display asymmetry (Fig. 60.14) [21, 24]. Various reports have stated that when recurrence of pigmentation is confined to the scar, this is a sign of benignity, such as recurrent nevi. Usually pigmentation of recurrent nevi develops for a limited period and stabilizes, sometimes even fading over time [25].

Recurrent nevi occur more frequently in females under the age of 40 years and in lesions excised on the back, followed by the abdomen and extremities [22, 26]. Usually the pigmentation

Fig. 60.14 Recurrent nevus

recurs within 6 months after the initial procedure [22, 27]. The majority of recurrent nevi may be observed after removal of ordinary nevi, followed by dysplastic nevus [22, 26]. Additional studies have shown that in 23% of cases of recurrent nevi the primary lesion appeared to be completely removed in the histopathologic report [22] and that only 75% of recurrent nevi had previous positive margins [26].

The most important differential diagnosis with recurrent nevi is recurrent melanoma (Tables 60.1 and 60.2) [25]. With the objective of studying the diagnostic differences between these lesions, a multicenter study was conducted in 2014 [28]. The authors found that patients with recurrent melanoma had a longer time interval between the procedures (median 25 months), while recurrent nevi occurred more quickly (median 8 months) [28]. Also, to help differentiation between both entities, the study defined dermoscopic characteristics for recurrent nevi and recurrent melanomas. Recurrent nevi were characterized by radial lines, symmetry, and a centrifugal growth pattern. Meanwhile, recurrent melanomas showed eccentric pigmentation at the periphery, a chaotic and noncontinuous growth pattern, and pigmentation beyond the scar's edge. In addition, it was found that recur-

Table 60.1 Clinical differences between recurrent nevi and melanoma [23–25, 28]

Recurrent nevi	Recurrent melanoma
Usually occurs with 6 months of the procedure	Usually occurs within a longer interval (median 24 months)
Usually fades over time	Progressive growth

Table 60.2 Dermoscopic differences between recurrent nevi and melanoma [23–25, 28]

Recurrent nevi	Recurrent melanoma
Pigmentation within scar area	Pigmentation extends beyond scar's edge
Centrifugal growth pattern	Chaotic growth pattern
Segmental Radial lines	Circles (especially visualized in facial lesions)
Symmetry	Asymmetry
–	Eccentric pigmentation at the periphery

rent melanomas may display a circular pattern; however, most lesions included in this subgroup were on the face, a possible confounder [28]. Also, authors found that the presence of globules and heterogeneous pigmentation were the strongest dermoscopic findings related to recurrent nevi, followed by irregular network and absence of streaks [28].

Another differential diagnosis to recurrent nevi is reactive pigmentation. This entity tends to extend perpendicular to the main axis of the scar, and shows a regular pigmented network and thin continuous streaks [29].

Three zones may be seen in histology: intraepidermal alterations that can be mistaken for melanoma, as a junctional melanocytic component with varying degrees of pigmentation; fibrotic scar tissue; and below this, the residual intradermal component of the melanocytic lesion may be seen [21]. It is possible to observe a histologic overlap with primary melanoma in some cases, especially when a retiform epidermis and atypical features are found, such as a confluent growth pattern, pagetoid spread, and cytologic spread [22].

Immunohistochemical analysis may be useful to help differentiate atypical recurrent nevi and melanoma. In recurrent nevi, labeling for gp100 (with HMB-45) is strong only in the junctional portion, while in melanomas it is found to be strong in both the junctional and deep dermal components [31]. Furthermore, tyrosinase and Ki-67 demonstrate a maturation pattern in recurrent nevi, whereby the strongest labeling is seen in the junctional component, with a progressive reduction throughout the dermis. The Ki-67 junctional proliferation rate is also found to be less than 5%. By contrast, melanoma expresses tyrosinase throughout the whole lesion and the proliferation rate is much higher [30].

Diagnosis To confirm the exact diagnosis of a recurrent nevus and exclude the possibility of recurrent melanoma, it is recommended to review the original histopathologic slides [21]. The importance of analyzing the first original sections lies in the fact that in only 67% of cases is it possible to correctly predict the original melanocytic lesion [26].

Therapeutic Approach In cases where there is no previous histopathologic diagnosis, excision and histopathologic examination are mandatory to rule out melanoma. With the confirmation of a benign nevus, no further treatment is necessary.

Whenever melanoma is suspected or the diagnosis is unclear, the lesion should be completely excised [21]. Partial biopsies may be problematic when trying to differentiate recurrent nevi from atypical melanocytic proliferations and melanoma. Cases in which biopsies were thought to represent recurrent nevi but the re-excised lesion showed unequivocal melanoma have been described [22].

Atypical Nevus

Concepts Atypical nevi, also known as Clark nevi, are benign melanocytic lesions that may share clinical and dermoscopic features with melanoma [31]. To date, the correct terminology between atypical and dysplastic nevus has been controversial. Often the term "atypical nevus" is clinically used to describe potentially suspicious lesions, which could present with histologic dysplasia. However, there is not always a clinical and histologic correlation [32, 33]. Therefore, many authors encourage the use of the term "atypical nevi" in the clinical setting, while "dysplastic nevi" is used as a histologic description [21, 34].

In 1992, an expert panel organized by the NIH Consensus Development Conference proposed abandoning the term "dysplastic nevus" and reinforced the terms "atypical nevus" [35]. This approach was justified based on two common errors: viewing different grading steps of dysplasia as a progression toward melanoma or stating that dysplastic nevus would be a "premalignant lesion" [32]. Many have even advocated the term "Clark nevus" to honor its first descriptor, as referred below, and to reaffirm the idea that it is simply a nevus variant [32]. In addition, many also use the term "nevus with architectural disorder" [32].

The first description regarding atypical nevi and melanoma was introduced by Clark and coworkers in 1978, termed the B-K mole

syndrome [36]. The letters B and K stood for the initials of the two affected families [36]. Later, Lynch et al. characterized the familiar atypical multiple mole melanoma syndrome (FAMMM), referring to patients with a similar phenotypic nevus in a melanoma-prone family [37]. In addition, Elder et al. [38] described the "dysplastic nevus syndrome" with familiar and sporadic variants. Later on, Rigel et al. [39] created a melanoma risk classification for patients with dysplastic nevus syndrome, according to their personal and family history of melanoma. Thus, both groups showed that there is a broad melanoma risk spectrum regarding this syndrome, ranging from isolated cases of individuals with only atypical moles to the description of FAMMM syndrome [40].

The exact prevalence of dysplastic nevus is unknown, because the majority of studies do not include histologic confirmation. Regarding the clinical classification, the estimated frequency of atypical nevi is 2–10% of the population [21, 41].

Diagnosis Atypical nevi usually appear during puberty, although they may develop throughout life [32]. Often atypical nevi are located in intermittently sun-exposed areas, such as the trunk and extremities. However, they may also appear in sun protected areas [31].

Many clinical criteria for atypical nevi overlap with those of early melanomas [21]. Tucker et al. clinically defined atypical nevus characteristics: variable pigmentation, irregular or asymmetric outline, indistinct borders, diameter over 5 mm, and a macular component [42].

Analyzing dermoscopic aspects, Hoffman-Wellenhof et al. identified six patterns, including reticular, globular, homogeneous, reticulo-globular, reticular-homogeneous, and globular-homogeneous (Fig. 60.15). Additionally the distribution of pigmentation was classified into six groups: central hyperpigmentation or hypopigmentation, eccentric peripheral hyperpigmentation or hypopigmentation, and multifocal hyperpigmentation or hypopigmentation. Similarly to common nevi, the authors found that most individuals had one predominant type of
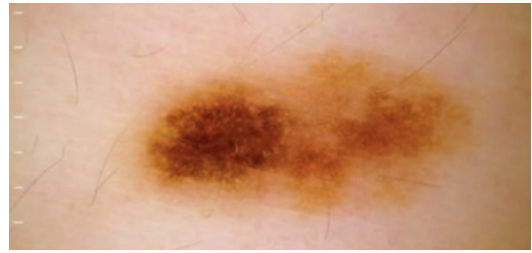
Fig. 60.15 Dermoscopy of atypical nevus

atypical nevi, also known as the signature nevi. Moreover, it was observed that eccentric peripheral hyperpigmentation is a rare (7.5%) finding in atypical nevi and should be evaluated to rule out melanoma [43].

Atypical nevi may be observed as isolated lesions or also can occur in the "atypical or dysplastic mole syndrome," which presents a broad clinical spectrum. Patients may have atypical/dysplastic nevus with no personal or family history of melanoma, while others may present with FAMMM syndrome [31]. According to the NIH Consensus statement published in 1992, the diagnosis of FAMMM or dysplastic nevus syndrome requires: occurrence of melanoma in one or more first or second degree relatives; presence of a large quantity of nevi (>50), some of which are clinically atypical; and nevi with distinct histologic features [35]. Compared with the general population, FAMMM carriers have a 150-fold greater risk of developing melanoma.

Histologic criteria for classification of dysplastic nevus may be divided into architectural and cellular [21]. Regarding architectural aspects, atypical nevus may display irregular nests at the junctional zone, bridging (horizontal anastomosis) between these nests, and the "shoulder phenomenon," which occurs when junctional nests extend beyond the dermal component [21]. Furthermore, lamellar or concentric fibroplasia (a dense extracellular matrix around the epidermal ridges) may be observed, as well as initial migration of single cell elements or nests through the epidermis [21]. At the cellular level, atypical melanocytes, nuclear polymorphism, and shift of the nucleus/plasma ratio may be seen [21].

In an attempt to standardize the histologic classification of dysplastic nevus, the World Health Organization enumerated major and minor criteria [44]. For establishment of the diagnosis it is necessary to have both major criteria and at least two minor criteria [44]. The major criterion is basilar proliferation of atypical melanocytes, which must extend at least three rete ridges beyond the dermal component and organization of this proliferation in a lentiginous or epithelioid-cell pattern. The minor criteria include the presence of lamellar fibrosis or concentric eosinophilic fibrosis, neovascularization, an inflammatory response, and the fusion of rete ridges [44].

There is controversy over whether dysplastic nevi may be melanoma precursors, as it is known that most do not progress to melanoma [21, 34]. Tsao et al. estimated the individual risk of a nevus (including a dysplastic nevus) transforming to melanoma is 1 in 10,000 during a lifetime [45]. In addition, only 20–30% of melanomas arise from nevi [46]. Of these nevus-derived melanomas, it appears that the incidence between common and dysplastic nevus is similar [47].

However, it is well established that atypical nevus is a phenotypic risk marker for melanoma [32]. The presence of atypical nevus, regardless of the total number of moles, increases the melanoma risk ten-fold compared with their absence [41].

Therapeutic Approach Prophylactic excision of atypical nevi is not indicated, since there is lack of evidence that the procedure reduces melanoma risk [48, 49, 50]. Also, unnecessary excisions increase costs and morbidity. Atypical lesions should only be removed when there is doubt regarding its differential diagnosis with melanoma [34, 49]. As in common nevi, atypical nevi may be removed by several techniques such as elliptical resection, shaving, or cauterization. Whenever possible, full excision should be attempted, so that the whole lesion can be assessed histologically. Therefore, a narrow excisional biopsy with 1- to 3-mm margins beyond the clinically visible pigmentation is recommended, as well as a depth sufficient to avoid transection [34]. It is known that dysplastic nevus may demonstrate heterogeneous histopathology and that melanoma may be missed through a sampling error [34, 51]. When these techniques are not possible, it is acceptable to carry out incisional punch biopsy or shaving of a more suspicious dermoscopic area [34].

The necessity of re-excision of dysplastic nevus is very controversial and there are no strong and formal recommendations. Some physicians decide to re-excise to prevent recurrence and the pseudomelanoma phenomenon. However, greater consensus exists regarding re-excision of severely dysplastic nevus, independently of margins, because of the difficulty of distinguishing it from melanoma [49]. In 2014, a panel of specialists summarized the results of several studies and established management recommendations for atypical nevus/dysplastic nevus [52, 53]. This report, authors stated that: (1) mildly and moderately dysplastic nevus with clear margins do not need to be re-excised; (2) mildly dysplastic nevus with positive margins and without clinical recurrence may be observed; (3) moderately dysplastic nevus with positive margins and without clinical recurrence possibly may be observed, although there is a lack of more formal data to verify this recommendation; (4) in cases with severe dysplasia and positive margins, re-excision is recommended with a 2–5-mm clinical margin [52, 53].

The follow-up of patients with atypical nevus includes clinical and dermoscopic evaluation every 3–6 months, which can be spaced to semi-annually or annually if lesions remain stable [54]. Patients who are at higher risk, such as those with multiple atypical lesions and personal or family history of melanoma, benefit from total body photography and digital dermoscopy [31, 54]. In addition, patients should be advised to perform self-examinations periodically and to use regular sun protection. In patients with dysplastic nevus syndrome or FAMMM, some consensus indicates annual eye examination, as there could be a greater risk of developing ocular melanoma.

Glossary

Cryotherapy A technique that uses an extremely cold liquid or instrument to freeze and destroy abnormal skin cells that require removal.

Electrolysis Electrochemical process whereby current is passed between two electrodes through an ionized solution (electrolyte) to deposit positive ions (anions) on the negative electrode (cathode) and negative ions (cations) on the positive electrode (anode). It is used for removing unwanted hair by destroying the hair root.

Hydroquinone An aromatic organic compound that is a type of phenol, having the chemical formula $C_6H_4(OH)_2$. It is prescribed to reduce pigmentation of the skin in certain conditions whereby an excess of melanin causes hyperpigmentation.

HMB-45 A monoclonal antibody that reacts against an antigen present in melanocytic tumors such as melanomas. The use of immunohistochemistry with melanocytic markers such as HMB-45 and Melan A, increases the detection rate of micrometastases.

Ki-67 The Ki-67 protein (also known as MKI67) is a cellular marker for proliferation. It is strictly associated with cell proliferation.

Leptomeningeal melanocytosis The excessive deposit of melanin by increasing the number of melanocytes, usually seen as a signal in the convexities of subarachnoid spaces, or brain parenchyma such as cerebellum, temporal lobes, pons, and medulla on noncontrast images.

Melanocytic A type of lesion that contains nevus cells (a type of melanocyte).

Peeling Peeling skin, called desquamation in medical terms, can be caused by different conditions. Very often, skin peels following chemical, thermal, or sunburn, with the latter being the most common cause.

Pseudopodia Cytoplasmic structures found in some eukaryotes. Pseudopods are one of the three locomotion modes of unicellular organisms (together with flagella and cilia). Pseudopods can also capture prey by phagocytosis.

Tyrosinase An oxidase that is the rate-limiting enzyme for controlling the production of melanin.

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Suggested Literature

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Pruritus

61

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and Fernanda Oliveira Camozzato

"Itch is an unpleasant sensation which evokes the desire to scratch"

Samuel Hafenreffer, 1660

Key Points

- Pruritus is the most common dermatologic symptom and is the main symptom of several dermatoses; it also frequently occurs in systemic diseases
- It may manifest many years before systemic diseases, including malignant ones. In some cases, it is the first symptom of malignant systemic diseases
- Several etiopathologic mechanisms may cause pruritus with peripheral or central origin
- Patient assessment includes complete clinical history, detailed history of pruritus, and additional tests
- Patient management requires treatment of symptoms and underlying diseases
- Providing follow-up and orientation is essential in the management of patients with chronic pruritus. Psychological assessment is required for these patients.

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Concepts

Pruritus was defined by Samuel Hafenreffer in 1660 as an unpleasant sensation that causes the desire or reflex to scratch [1]. This condition is the most frequent symptom of dermatologic diseases and also the one that better defines these diseases; additionally, it may be present in several systemic diseases. Pruritus may be disseminated or localized, affecting the skin surface; the squamous epithelium of the conjunctiva, mouth, nose, pharynx, and anogenital region; and the ciliated epithelium of the trachea [2, 3]. This symptom may be intense, even when patients have no visible skin changes. Pruritic areas around the primarily stimulated site that itch even after very weak stimuli are defined as areas of alloknesis [4].

Pruritus may be acute or chronic, the latter occurring, by definition, when the symptom lasts for 6 months or more [5]. Acute pruritus, because it occurs with pain, is a defense mechanism against external harmful agents. Chronic pruritus is difficult to ignore, leading to difficulties concentrating, sleep disorders, absence from school or work, and sometimes suicide attempts in patients with more severe symptoms [3, 6]. Additionally it is associated with a considerable reduction in quality of life and may be as debilitating as chronic pain [7].

In addition to biological pruritus, triggered by several chemical mediators, itch may be also a psychosocial manifestation resulting from mechanisms of frustration, similar to what happens in nonhuman social animals (grooming) [8].

Epidemiology

Statistical data on the epidemiology of pruritus are scarce, possibly leading to an underestimation of its prevalence. This is because many studies, especially those outside the field of dermatology, do not collect data on pruritus, even when the symptom is considered as relevant by patients.

Pruritus is more common in women than in men and is more frequently diagnosed in Asians than in Caucasians [9–11]. The prevalence of pruritus increases with age, because the elderly population not only usually presents with xeroderma but also has a higher prevalence of systemic problems that cause pruritus [12, 13]. Pruritus is more prevalent among individuals of low socioeconomic status and low income [9].

A cross-sectional study including almost 19,000 adults found a prevalence of 8–9% of acute pruritus in the study population [9] and an association between pruritus and chronic pain [14]. Recent research shows that the prevalence of chronic pruritus is around 13.5% in the general adult population [10] and around 16.8% in a sample of company employees attending a routine medical appointment [12]. In a study of 18,137 individuals with skin diseases, 42% reported having pruritus [15].

Few studies evaluated the frequency of pruritus in the primary health care setting. According to data from the Bettering the Evaluation and Care of Health (BEACH) Program for the Australian population, pruritus is the main complaint at 0.6% of medical visits, excluding perianal, periorbital, or auricular pruritus [16]. The Fourth National Study of Morbidity Statistics from General Practice [17], conducted in Great Britain with 502,493 patients, found that pruritus and related conditions are reported in 1.04% of appointments (0.73% for men and 1.33% for women).

The origin of pruritus, whether dermatologic or systemic, could not be established in 8–15% of patients [13]. However, in systemic diseases that cause pruritus its prevalence may be very high, as is the case with hemodialysis patients, who may present with pruritus in up to 90% of cases [18]. This symptom may be present in up to 50% of patients with cholestasis, in 80–100% of those with primary biliary cirrhosis, in up to 80% of those with cutaneous T-cell lymphoma, in up to 50% of those with polycythemia vera, and in up to 30% of those with Hodgkin's lymphoma [6]. In dermatologic diseases, the frequency of pruritus is relevant and depends on the underlying disease; it is present, for example, in all patients with urticaria and atopic dermatitis [19].

Classification

Pruritus may be of peripheral or central origin, and the perception of this symptom depends on the neurophysiologic and psychological changes it causes. Patients may report different sensations to define pruritus, such as itch, bite, tingle, perforation, pinch, and burn [6].

A neurophysiologic classification of the type of pruritus was proposed and is important both for patient management and for understanding of disease mechanisms. More than one form of pruritus may coexist in the same patient, for example, atopic individuals who present with neurogenic and pruritoceptive pruritus. In 2003 Twycros et al. [3] proposed a neurophysiologic classification:

(a) Pruritoceptive or dermal pruritus: induced by stimulation of C-nerve fibers by different pruritogens. It originates in the skin and may be caused by inflammatory mechanisms, xeroderma, or direct skin damage. It is present in scabies, urticaria, and insect bites

(b) Neuropathic pruritus: resulting from lesions at any point of the afferent nervous pathway,

such as occurs in postherpetic neuralgia, multiple sclerosis, and brain tumors

(c) Neurogenic pruritus: of central origin, but there are no lesions to nervous fibers. It results from an increase in the concentration of endogenous opioids, as in cholestasis and after the administration of exogenous opioids

(d) Psychogenic pruritus: triggered by psychiatric diseases such parasitophobia or by psychological factors such as anxiety disorders

Another classification of pruritus was defined by the International Forum for the Study of Itch (IFSI) in 2007 [5]. This classification is divided into two parts and gives priority to the clinical manifestations of pruritus, distinguishing between disorders with or without skin lesions and whether these lesions are primary or secondary.

In the first part of classification, three groups of conditions are defined according to history and symptoms in the skin of patients with pruritus.

– *First group*: includes pruritus in primary skin diseases represented by pruritic dermatoses (inflammatory, infectious and autoimmune diseases, genodermatosis, reaction to drugs, dermatoses of pregnancy, and skin lymphomas), all of which lead to specific skin changes

– *Second group*: includes pruritus in normal skin resulting from systemic diseases (endocrine, hematologic and metabolic disorders, infections, lymphoproliferative diseases, solid neoplasms, neurologic diseases, psychiatric diseases, and drug-induced pruritus)

– *Third group*: includes chronic lesions secondary to scratching, such as prurigo nodularis or simple chronic lichen

In the second part of the classification, patients were categorized according to their underlying disease, which was divided into several categories:

I. Dermatologic disease: pruritus caused by "skin diseases" such as psoriasis, atopic dermatitis, dry skin, scabies, or urticaria

II. Systemic disease: pruritus caused by "systemic diseases" other than those affecting the skin, such as hepatic diseases (primary biliary cirrhosis), renal diseases (chronic kidney disease), hematologic diseases (Hodgkin's disease), and multifactorial causes such as metabolic or drug-induced

III. Neurologic disease: pruritus caused by "diseases of the central or peripheral nervous system" such as nerve compression, nerve damage, or nerve irritation

IV. Psychogenic or psychosomatic disease: pruritus caused by "psychiatric or psychosomatic disease"

V. Mixed: pruritus caused by the overlap and coexistence of several diseases

VI. Pruritus of undetermined origin

This classification aims to avoid unnecessary laboratory and imaging studies, as is the case in patients with typical clinical history suggestive of dermatosis-induced pruritus, when usually there is no need for further investigation.

Neurophysiology

The neuronal basis of the mechanisms underlying pruritus is complex and has been elucidated by new discoveries in the field. Skin, conjunctiva, and mucosa are the peripheral tissues that may produce a sensation of pruritus. In the skin, sensory nerves innervate epidermis, dermis, and subcutaneous adipose tissue. Free nerve endings for pruritus are located mainly at the dermoepidermal junction [20]. Electrophysiology studies of peripheral nerves in humans and animal models show that the chemical mediators of pruritus elicit action potentials in a subset of nociceptors, the pruriceptive nociceptive neurons (or pruriceptors), which are mainly amyelinic C fibers [21].

Pruritoceptors carry impulses toward the dorsal horn of the spinal cord, where they make a synapse with the secondary neuron. The axons of this neuron cross to the contralateral spinothalamic tract (STT) through the anterolateral funiculus and continue into the thalamus to terminate in the somatosensory cortex, reaching areas involved in the processes of evolution, sensation, emotion, reward, and memory, which are superposed to the areas

activated by painful stimuli [22]. The transection of this ascending pathway impairs itch as well as pain and temperature sensations [23].

Electrophysiologic studies of the neurons of the STT in animal models show that nearly two-thirds of the nociceptive neurons of this tract are not pruritogenic and the other third is. Nonpruritogenic neurons of the STT are activated by mechanical stimuli, heat, or capsaicin, and pruritogenic neurons are activated both by painful stimuli such as heat or capsaicin and by pruritic stimuli such as histamine. It is still unclear whether there are specific pruritogenic neurons, i.e., that transmit only the sensation of pruritus [24, 25]. However, a recent study found that, in a genetically engineered mouse with restricted expression of the capsaicin receptor, selective activation of a class of pruriceptors by capsaicin elicits itch-like and not pain-like behavior, showing that there may be a neurologic distinction between nerve cells that cause pain and cells that cause itching [26].

As a hypothesis, itch may result from activity in the pruriceptive neurons in the absence of sufficient activity in nonpruriceptive neurons. The neural circuitry hypothesized to evaluate the relative activity in pruriceptive and nonpruriceptive neuronal populations and to decode itch from pain is unknown, but is likely to reside in suprasegmental regions of the brain [21].

Mediators of Pruritus

Pruritus is triggered by pharmacologic mediators that act on nerve endings, the so-called pruritogenic agents. These pruritogens may be located both peripherally and centrally, and many of them act synergistically, by means of a myriad of mechanisms summarized in Table 61.1.

Histamine is the main peripheral mediator of pruritus, having been acknowledged for more than 60 years, and is secreted by degranulated mast cells and circulating basophils. This substance causes pruritus by directly stimulating nerve endings and also by interacting with H1 receptors present in C fibers [27], leading to vasodilation and edema [27]. There are other histamine receptors, such as H2 and H3, but these are not linked to the mediation of pruritus, although there has been

Table 61.1 Itch mediators and corresponding antipruritic agents

Mediators of pruritus	Antipruritic agent
Histamine	Antihistamines
Serotonin	Paroxetine, fluoxetine, mirtazapine, sertraline, citalopram, ondansetron
Substance P	Aprepitant
Prostaglandins	Nonsteroidal anti-inflammatory drugs, aspirin
Opioids	Naloxone, naltrexone, nalfurafine, butorphanol
TRPV1 receptor	Capsaicin
TRPM8 receptor	Menthol
Interferon-α	Thalidomide
GABA (γ-aminobutyric acid)	Gabapentin, pregabalin
Acetylcholine	Doxepin, oxybutynin
Leukotrienes	Zafirlukast, zileuton

Adapted from Hassan and Haji [118]

an improvement of pruritus in patients with urticaria with the use of some H2 blockers. Histamine type 4 receptor (H4), present in dendritic cells, mast cells, and eosinophils, is involved in allergic inflammation [28] and also may be involved in the mediation of pruritus, making this receptor a possible new target in the management of pruritus, especially in atopic dermatitis [28]. The role of histamine in pruritic diseases such as urticaria, reactions to insect bites, skin mastocytosis, and some drug eruptions has already been established [2, 3]. However, this substance is not the main pruritogenic agent in systemic diseases, which is evidenced by the low response of patients with these diseases to antihistamine therapy [29].

Serotonin is a less potent pruritogenic agent than histamine. Its peripheral action is due to the release of histamine from mast cells [30], and its central action probably involves the neurotransmitter system of opioids and the activation of $5HT_3$ receptors, which are not found in the skin. Serotonin is also found in great amounts in platelets, a fact that may explain the presence of pruritus in hematologic diseases with platelet involvement [3].

Substance P is synthesized in the body of C-type neurons and transported through peripheral nerve endings. Intradermal injection of substance P causes pruritus, edema, and erythema, resulting in the release of tumor necrosis factor α (TNF-α),

leukotriene B4, histamine, and prostaglandin D2 [31]. In atopic dermatitis, serum levels of substance P are elevated and correlated to disease severity [32]. This neuropeptide acts through the neurokinin 1 (NK1) receptor pathway. A study conducted by Costa et al. showed that aprepitant, the NK1 receptor antagonist, was tested as a potential antipruritic agent in Sézary syndrome [33]. Depletion of this substance by capsaicin is one of the mechanisms of controlling pruritus and pain [24].

Prostaglandins, considered in isolation, are not pruritogenic agents, but may potentiate the effect of histamine and of other mediators of pruritus [35]. The use of cyclooxygenase inhibitors does not improve pruritus in the general patient population, but appears to be useful in patients with human immunodeficiency virus (HIV). The use of aspirin improves pruritus in patients with polycythemia vera, probably due to the action of this drug on platelet adhesiveness rather than on the formation of prostaglandins [36].

Cytokines: The involvement of *interleukin 2* (IL-2) in the development of pruritus is based on the observation of generalized pruritus in patients using high doses of recombinant IL-2 for the treatment of cancer [37]. Patients with atopic dermatitis using cyclosporine, an IL-2 inhibitor, experience a considerable relief of pruritus. It is not clear whether this process is directly mediated by receptors or indirectly mediated by mast cells and endothelial cells. High levels of *interleukin-31* (IL-31) are present in the skin of patients with atopic dermatitis and prurigo nodularis, indicating that this substance may be a possible cause of pruritus in patients with these conditions [38, 39].

Opioid peptides may trigger pruritus by leading both to degranulation of mast cells and activation of opioid receptors, either central or peripheral. Intradermal morphine causes pruritus, which may be inhibited by topic pretreatment with doxepin (H1 antihistamine agent) [40] but may be only partially inhibited by the μ-receptor antagonist (naloxone). Intraspinal μ-opioid agonists induce segmental pruritus, a condition that may be inhibited by μ-receptor antagonists [41], but is not affected by antihistamines [41]. Additionally it has been demonstrated that the stimulation of κ-opioid receptors blocks the effect of μ-receptor agonists [42], showing that

opioid-induced pruritus may be the balance of the interaction between the system of receptors μ and κ. Opioid peptide antagonists have been used in the treatment of pruritus-associated diseases in chronic kidney disease and cholestasis.

Proteolytic enzymes: Human mast cells produce two proteases: tryptase and chymase. These enzymes act on G proteins coupled to PAR-2 receptors expressed in afferent C-fiber neurons [43]. When activated, these fibers secrete substance P, which activates mast cells, thus closing the cycle that stimulates pruritus [4]. Upregulation of PAR-2 receptors has been observed in patients with atopic dermatitis [43].

Transient receptor potential channels (*TRP*): These molecules are calcium-permeable channels that sense temperature, osmotic, and mechanical changes. TRPV1 is present on nociceptive C neurons and is activated by capsaicin and endogenous substances (endovanilloids). Other TRPVs (TRPV2, TRPV3, TRPV4, TRPM8) are activated at specific temperatures [44]. Evidence suggests that TRPV1 is a fundamental integrating element in pruritic and pain pathways. It has been discovered that sensory neuronal activation by histamine and PAR2 receptor also involves the activation/sensitization of TRPV1, that TRPV1 expression is amplified in keratinocytes of prurigo nodularis, and that stimulation of TRPV1 channels releases multiple pruritoceptive mediators such as interleukins and neuropeptides [45]. It has been postulated that TRPV3 might be a regulator and/or cotransducer of TRPV1-mediated pruritus and pain. A study by Stokes et al. [46] showed mast cell degranulation upon thermal and physical activation of TRPV2. In addition, mast cells also express TRPV1 and TRPV4. TRP melastatin 8 (TRPM8) is expressed selectively by C-type neurons. Menthol and its analogs as well as icilin stimulate TRPM8 [47];

Neurotrophin and nerve growth factor (*NGF*) is overexpressed in prurigo nodularis and its therapeutic administration is pruritogenic [48]. In atopic dermatitis, NGF is released by keratinocytes, mast cells, and fibroblasts, and plasma levels of NGF are also elevated and correlate with disease activity [49]. In addition, expression of neurotrophin-4 is elevated in the cutaneous lesions of patients with atopic dermatitis and prurigo nodularis [48, 49].

Endocannabinoids and cannabinoid receptors: Cannabinoid receptors are expressed on skin nerve fibers and may have a role in pruritus. For instance, cannabinoid receptor (CB1) agonist HU210 diminishes histamine-induced excitation of nerve fibers and thereby reduces itching. [50] This suggests that CB1 signaling may be involved in initiation of itch.

Corticotropin-releasing hormone (*CRH*) and its analog, urocortin, lead to histamine release upon intradermal injection [51]. CRH is also involved in mast cell degranulation occurring during periods of acute stress. The exact function played by leukotrienes in itch is unclear. Studies have reported the use of leukotriene receptor antagonists zileuton and zafirlukast for antipruritic action in atopic dermatitis [52]

Calcitonin gene-related peptide: Many neurons of the dorsal root ganglion coexpress substance P, calcitonin gene-related peptide (CGRP), and PAR2. CGRP plays a modulatory role in inflammation and pruritus. It would seem that CGRP has an inhibitory effect on substance P-induced itching as it prolongs itch latency following injection [53], but increased levels of CGRP are seen in atopic dermatitis, nummular eczema. and prurigo nodularis [53]. Like substance P, CGRP-mediated itch may result from mast cell activation.

Acetylcholine (*ACh*) is a neurotransmitter which binds to both muscarinic and nicotinic receptors. In mice, activation of the muscarinic M3 receptors causes pruritus [54]. Intracutaneously injected ACh caused itch in atopic eczema [55]. Histamine-sensitive as well as histamine-insensitive C-nerve fibers are stimulated by ACh. Atopic dermatitis patients are more sensitive to ACh and less sensitive to histamine than normal subjects [54].

Clinical Presentation

Pruritus in Systemic Diseases

In systemic diseases, the skin may appear normal or have skin lesions induced by scratching, and a diagnosis may be difficult to establish. In these cases pruritus is usually symmetric and extensive and has an insidious onset; in addition, its intensity is not directly related to the severity of under-lying disease. Moreover, localized forms may be transformed into generalized forms during disease progression. Only 50% of patients complaining of pruritus and without apparent dermatologic lesions at the time of the medical visit have its etiology identified [56], showing that pruritus may precede the diagnosis of the underlying disease by years.

There are many etiologic hypotheses for the several manifestations of pruritus in systemic diseases, some of which have not yet been confirmed. This is one of the main reasons why the treatment of this symptom is still difficult and often does not give a definitive solution for the patient. Patient follow-up and a good doctor–patient relationship are essential to manage this symptom, which in most cases is extremely debilitating and has no curative treatment. Symptoms are summarized in Table 61.2.

Table 61.2 Systemic diseases that can induce pruritus (examples)

Metabolic and endocrine diseases	Chronic renal disease
	Liver diseases with or without cholestasis
	Hyperparathyroidism
	Hyper- and hypothyroidism
	Carcinoid syndrome
	Iron deficiency
Infective diseases	HIV and AIDS
	Parasitoses
Hematologic disorders	Polycythemia vera
	Leukemia
	Lymphoma (Hodgkin's lymphoma, cutaneous lymphoma)
Neurologic diseases	Multiple sclerosis
	Brain tumors
	Notalgia paresthetica
	Brachioradial pruritus
	Postzosteric neuralgia
Psychiatric or psychosomatic diseases	Depression
	Affective disorders
	Hallucinosis
	Obsessive and compulsory disorders
	Schizophrenia
	Eating disorders

Adapted from Weisshaar et al. [85]

Pruritus in Chronic Kidney Diseases

The pathophysiology of pruritus associated with chronic kidney diseases is unknown. However, some mechanisms have been suggested, including skin conditions such as moderate to severe xeroderma, dialysis, medications taken by the patient, metabolic factors, dysfunction of peripheral or central nerves, involvement of opioid receptors (μ and κ), and microinflammation in uremia [57, 58]. Pruritus is not related to the etiology of renal failure nor to age, gender, skin color, or time on dialysis.

The number of mast cells is greater in uremic patients than in normal patients [59], and the skin of uremic patients produces several pruritogenic cytokines that stimulate the nerve endings of fibers carrying the sensation of pruritus. Additionally an increase in the concentration of calcium, magnesium, phosphates, and mast cells was observed in hemodialysis patients with symptoms of pruritus [57]. Although plasma concentrations of histamine are higher in uremic patients than in nonuremic patients, these values are not related to the severity of pruritus, and antihistamines did not resolve the symptoms. Serum serotonin is high in hemodialysis patients; however, randomized, placebo-controlled, double-blind trials did not observe an improvement in pruritus among patients treated with ondansetron, an antagonist of $5HT_3$ receptors [60]. Studies obtained controversial results on the improvement of chronic kidney disease-associated pruritus with the use of opioid antagonists. Ultraviolet B (UVB) phototherapy has been used with good results. Systemic changes resulting from dialysis, such as decreased erythropoietin, and hyperparathyroidism were also related to pruritus and should be corrected in patients with these conditions.

A total of 22–90% of patients with severe renal failure complains of pruritus, especially those who are undergoing dialysis. This complaint has declined in recent years, probably due to the use of highly permeable membranes during dialysis. Patients with more intense pruritus have worse prognosis for renal disease and have higher mortality rates.

Pruritus in Liver Disease

Pruritus is a frequent symptom in patients with liver diseases caused by cholestasis, mechanical obstruction, metabolic disorders, or inflammatory diseases [62], and is less frequent in patients with infectious liver disease (hepatitis B or C) or alcoholic liver disease.

Pruritus is an initial symptom of cholestasis and affects 20–50% of patients with jaundice; additionally its intensity is not related to the severity of cholestasis. The onset of this type of pruritus occurs in the palmoplantar region, but most patients present with the generalized form, with symptoms worsening at night [63]. In addition to pruritus, these patients show postinflammatory hyperpigmentation on their back, which spares the central region, and the characteristic "butterfly" sign. Other clinical findings related to cholestasis may also be present, such as xanthelasma secondary to hypercholesterolemia, jaundice, ascites, and hepatomegaly. Sometimes pruritus is so intense that it leads the patient to think about suicide and becomes one of the indications for liver transplantation [62].

Diseases causing intrahepatic cholestasis that may lead to pruritus are primary biliary cirrhosis, pruritus gravidarum, sclerosing cholangitis, viral hepatitis, and drug-induced cholestasis. In primary biliary cirrhosis, pruritus occurs in almost 100% of patients and is the initial symptom of disease in nearly 50% of the cases. The symptom may be severe and may precede the diagnosis of primary biliary cirrhosis by years [64]. In pruritus gravidarum, pruritus occurs in the third trimester of pregnancy, being more common in multiple pregnancies. The symptom disappears immediately after delivery and may recur in subsequent pregnancies and with the use of oral contraceptives. Drug-induced cholestasis may be very symptomatic and may be caused mainly by phenothiazine, estrogens, and tolbutamide. Extrahepatic bile duct obstruction may also cause pruritus [2, 62].

Several hypotheses have been suggested to explain the cause of cholestatic pruritus, such as the stimulation of skin fibers by toxic bile salts, pruritogens derived from destroyed hepatic cells, changes in the metabolism of bile salts in the intestine, steroid hormones, accumulation of endogenous

opioids, and plasma accumulation of substances produced in the liver [65]. Recent studies showed that increased serum levels of autotaxin (ATX), the enzyme responsible for metabolizing lysophosphatidylcholine into lysophosphatidic acid (LPA) and increasing the levels of this acid, is a specific finding for cholestatic pruritus but not for other types of systemic pruritus [66]. Rifampicin significantly reduces the intensity of pruritus by decreasing ATX activity in patients with cholestatic pruritus. The therapeutic action of rifampicin may be partially explained by the binding of this drug to the pregnane X receptor, which inhibits ATX expression [66].

The treatment of cholestasis recommended in guidelines includes anion-exchange resins (cholestyramine), pregnane X receptor agonists, opioid antagonists (naltrexone, naloxone), and serotonin reuptake inhibitors (sertraline). In patients with severe pruritus and unresponsive to standard therapy, experimental approaches should be considered, such as UVB phototherapy, extracorporeal albumin dialysis, nasobiliary drainage, and liver transplantation [65].

Pruritus in Hematologic Diseases

Several hematologic diseases evolve into symptoms of pruritus, which are often severe. Most of these diseases are malignant, including tumors, bone marrow diseases, and lymphoproliferative diseases. The mechanisms leading to pruritus in these diseases may consist of toxic products released by the tumor, allergic reactions to the released components, and direct damage to brain nerves, in the case of tumors located in this area [67, 68].

Iron deficiency anemia: The most common symptom is generalized pruritus, with no direct relationship to the severity of anemia. Some patients may present with localized pruritus, especially in the vulvar and perianal regions. Laboratory abnormalities may be observed only for ferritin levels, with normal levels of serum iron. The causes of this deficiency should be investigated and corrected [69].

Polycythemia vera: Approximately 50% of patients with polycythemia vera complain of pruritus [70] characterized by the sensation of "biting" and usually triggered by contact with water (aquagenic pruritus). Pruritus may precede the

clinical disease by years. Studies suggest that the mechanism of pruritus in polycythemia vera is related to platelet aggregation leading to the secretion of serotonin and other pruritogenic agents [70]. Other studies show that the release of high levels of histamine resulting from the increased number of basophil granulocytes may trigger pruritus [68]. Pruritus appears to be more pronounced in patients with the JAK2V617 mutation [71].

Hodgkin's disease: Pruritus is present in up to 30% of patients with Hodgkin's disease and may precede the disease by up to 5 years [68, 69]. It is described as producing a burning sensation that usually becomes more severe at night, affects the lower half of the body, and tends to evolve into generalized pruritus. Dermatologic lesions may be present and resemble ichthyosiform changes. Patients with more severe pruritus and exhibiting poor therapeutic response are those with the worst prognosis of disease progression [69]. Several factors, such as the secretion of leukopeptidases and bradykinin, histamine, and high immunoglobulin E levels deposited in the skin, may contribute to pruritus in lymphomas [68, 69].

Leukemia: Pruritus is not a frequent complaint in patients with leukemia, but when present it is usually disseminated. Skin infiltrates may produce localized itch at the site of the lesion [69].

Systemic mastocytosis: Causative agents of degranulation of mast cells cause generalized pruritus in these patients [68].

Cutaneous T-cell lymphoma (*CTCL*) encompasses a diverse group of diseases characterized by malignant T lymphocytes that initially home to the skin. Mycosis fungoides is the most common variant and Sézary syndrome the rarest [72]. A characteristic hallmark of CTCL, especially Sézary syndrome, is pruritus, the sensation of itch which is repeatedly observed in various CTCL types [73, 74]. In an outpatient setting, approximately one-third of the patients with the diagnosis of CTCL complain of itch that accompanies the disease, and in some cases pruritus was the only symptom in a patient leading to the diagnosis of a CTCL [73, 74]. Pruritus as a symptom is almost invariably present in CTCL progressing into generalized erythrodermic mycosis fungoides and Sézary syndrome. It may be speculated that T cells homing to the skin provoke the release of inflammatory cytokines, but the precise

molecular mechanism is still unknown. Pruritus in CTCL seems to be both a blessing and a curse: a blessing in those patients in whom it may lead to early diagnosis, and a curse for those who are resistant to therapy. Further research is mandatory to unravel the molecular mechanisms and provide more specific treatment of pruritus in CTCL [75].

Pruritus in Endocrinologic Diseases

Pruritus is present in several endocrinologic diseases such as hyperthyroidism, hypothyroidism, diabetes mellitus, multiple endocrine neoplasia, carcinoid syndrome, and hyperparathyroidism [69].

Hyperthyroidism: Four percent to 11% of patients with thyrotoxicosis present with pruritus [76, 77]. Triggering mechanisms may include: (1) activation of kinins in the skin; (2) decrease of itch threshold due to vasodilation; and (3) changes of bile acids in the blood. The correction of disease improves pruritus, which may be the main complaint in some patients with hyperthyroidism.

Hypothyroidism: Pruritus is related to xeroderma, a characteristic symptom of patients with hypothyroidism. The use of emollients, as well as the correction of the underlying disease, improves the symptoms [76].

Diabetes mellitus: Nearly 3% of these patients present with pruritus. In this case, the mechanisms involved in the development of pruritus are peripheral neuropathy, uremia secondary to chronic renal failure, and anatomic dysfunction [78].

Carcinoid syndrome: Patients with carcinoid syndrome may present with pruritus combined with flushing, diarrhea, and cardiac symptoms [76].

Primary hyperparathyroidism: A substantial number of patients with primary hyperparathyroidism complain of pruritus [77]. The pathophysiology of pruritus in this disease is not well known, although these patients usually present with deficiency of vitamin D and minerals such as zinc, which may contribute to pruritus.

Pruritus in Psychiatric Diseases

Psychiatric diseases such as depression, anxiety, and some psychoses may include severe pruritus as one of their symptoms [6]. The accurate diagnosis of these patients is important, because treatment requires a psychiatric approach. In this case there are no primary skin lesions but rather lesions secondary to itching, ranging from superficial excoriations to major lichenifications. Currently it is estimated that one-third of patients seeing a dermatologist have emotional and psychosocial factors involved in their disease; however, there is still great reluctance to include psychiatric treatment as part of the management of dermatoses [3, 7]. It is extremely important to raise awareness of these diseases and to provide appropriate guidance to patients, despite their reluctance.

Pruritus in Neurologic Diseases

Neurologic diseases such as multiple sclerosis, focal lesions, tumors, abscesses, and stroke may include pruritus as part of their clinical picture. Localized neurologic lesions, such as tumors and brain abscesses, may result in unilateral pruritus.

Brachioradial pruritus: Located in the dorsal and lateral regions of upper limbs, this type of pruritus especially affects patients in the sixth decade of life and is more common in summer months, being classified by several authors as a photodermatosis. An investigation for associated neuropathies should always be made, because current studies show that up to 57% of these patients present with radiculopathies in the cervical region. Treatment with antihistamines, topical capsaicin, and topical corticosteroids may lead to an improvement in these patients. Therapy regimens for neuropathies may also relieve symptoms [79].

Pruritus in HIV Infection

Pruritus is a very common complaint in patients with HIV and is sometimes the first manifestation of disease. The intensity of pruritus may range from mild to very severe presentations. It is associated with most common dermatoses in patients with HIV, but may be present even when there is no dermatologic change. Pruritic dermatoses associated with HIV disease include pruritic papular eruption and eosinophilic folliculitis.

These dermatoses may be easily diagnosed through skin inspection and physical examination, and have a high positive predictive value for the diagnosis of HIV infection [80, 81].

In these patients, chronic pruritus may lead to skin changes such as excoriations, lichenification, prurigo nodularis, pigmentation changes, and secondary infection. Intense xeroderma is found in patients with AIDS and leads to a physicochemical action on the endings of C fibers in the skin. In addition, systemic complications such as liver diseases and renal failure may also worsen pruritus in these patients. Finally, the drugs used in the specific treatment of this disease often trigger pruritus [80].

Treatment of these patients includes the treatment of xeroderma, with the daily use of emollients and basic care to avoid the worsening of skin dryness.

Pruritus in Dermatologic Diseases

Dermatologic diseases often evolve into pruritus, which may be located in the area of skin lesion or sometimes be generalized. Many dermatoses cause this symptom, such as atopic dermatitis, urticaria, irritative and allergic contact dermatitis, seborrheic dermatitis, stasis eczema, prurigus, and lichen planus, but analyzing the specific approaches for these diseases beyond the remit of this chapter.

Pruritus Ani

Anal and perianal pruritus affects 1–5% of the general population in the proportion of four males to one female [82]. Its symptoms have an insidious onset and may last for years before the patient seeks treatment. This type of pruritus may be primary, with no apparent dermatologic lesion, or secondary to hemorrhoids, anal fistulas and fissures, psoriasis, contact eczema, lichen sclerosus, sexually transmitted diseases, parasitosis, and neoplasms. Primary causes include dietary factors such as increased intake of coffee, poor personal hygiene, and psychogenic dis-

eases. Anxiety and depression increase pruritus ani. Patients with mild pruritus ani respond to general care such as hip baths and cold compresses, avoidance of abrasives and soaps in the area, and corticosteroid therapy with low-potency corticosteroids [82]. Patients with severe pruritus require high-potency corticosteroids and sometimes topical immunomodulators such as tacrolimus [69].

Genital Pruritus

The characteristics of vulvar and scrotal pruritus are very similar to those of perianal pruritus. However, less than 10% of patients with genital pruritus symptoms present with psychogenic pruritus; thus, a detailed investigation should be conducted to find the triggering agent. The management of these patients is similar to that of patients with pruritus ani [69].

Scar Pruritus

During the time when scars are healing, which ranges from 6 months to 2 years, patients commonly present with pruritus triggered by nerve regeneration and chemical and physical stimuli. However, the formation of keloids and hypertrophic scars may prolong the duration of pruritus. The treatment is performed with emollients, topical and injectable corticosteroids, interferon, topical retinoids, gels, and silicone strips [69].

Drug-Induced Pruritus

Almost all drugs have the potential of inducing pruritus by several mechanisms; therefore, the use of medications should always be addressed in medical history taking [83]. Drugs may induce pruritus by causing skin lesions such as urticarial and morbilliform rash, by producing systemic changes such as hepatotoxicity or cholestasis, or by causing xeroma or phototoxicity [84]. Drugs that may induce or maintain chronic pruritus are listed in Table 61.3.

Table 61.3 Drugs that may induce or maintain chronic pruritus (without a rash)

Class of drug	Substance (examples)
ACE inhibitors	Captopril, enalapril
Antiarrhythmic agents	Amiodarone, disopyramide, flecainide
Antibiotics	Amoxicillin, ampicillin, cefotaxime, ceftriaxone, chloramphenicol, ciprofloxacin, clarithromycin, clindamycin, cotrimoxazole, erythromycin, gentamycin, metronidazole, minocycline, ofloxacin, penicillin, tetracycline
Antidepressants	Amitriptyline, citalopram, clomipramine, doxepin, fluoxetine, fluvoxamine, imipramine, lithium, mirtazapine, nortriptyline, paroxetine, sertraline
Antidiabetic drugs	Glimepiride, metformin
Antihypertensive drugs	Clonidine, doxazosin, hydralazine, methyldopa, prazosin, reserpine
Anticonvulsants	Carbamazepine, clonazepam, gabapentin, lamotrigine, phenobarbital, phenytoin, topiramate, valproic acid
Anti-inflammatory drugs	Acetylsalicylic acid, celecoxib, diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam
AT II antagonists	Irbesartan, telmisartan, valsartan
β-Blockers	atenolol, bisoprolol, metoprolol, nadolol, pindolol, propranolol
Bronchodilators, mucolytic agents, respiratory stimulants	Aminophylline, doxapram, ipratropium bromide, salmeterol, terbutaline
Calcium antagonists	Amlodipine, diltiazem, felodipine, nifedipine, nimodipine, verapamil
Diuretics	Amiloride, furosemide, hydrochlorothiazide, spironolactone, triamterene

Table 61.3 (continued)

Class of drug	Substance (examples)
Hormones	Clomifene, danazol, oral contraceptives, estrogens, progesterone, steroids, testosterone and derivatives, tamoxifen
Immunosuppressive drugs	Cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus, thalidomide
Antilipids	Clofibrate, fenofibrate, fluvastatin, lovastatin, pravastatin, simvastatin
Neuroleptics	Chlorpromazine, haloperidol, risperidone
Tranquilizers	Alprazolam, chlordiazepoxide, lorazepam, oxazepam, prazepam
Uricostatics	Allopurinol, colchicine, probenecid

Adapted from Weisshaar et al. [85]

Diagnosis

The first step in the therapeutic approach of pruritus is attempting to evaluate whether itch is attributed to a dermatologic cause or to an underlying disease. In a practical approach, patients with pruritus may be divided into the following groups: (1) patients with primary pruritic dermatologic disease; (2) patients with dermatologic lesions secondary to pruritus; (3) patients with pruritus and without dermatologic lesions [85]. In most cases, no systemic diseases are found in patients with generalized pruritus, who are classified as patients with pruritus sine materia [85, 86] (Tables 61.4 and 61.5).

In patients with pruritic dermatologic disease, the diagnosis and management of pruritus aims to treat the dermatosis [85–90]. However, in individuals who have no dermatologic lesions or in those whose lesions are secondary to scratching, a detailed assessment should be made, including patient's history, clinical characteristics of pruritus, thorough physical examination, laboratory screening, and imaging studies to investigate systemic diseases that cause pruritus [85–90].

Table 61.4 Clinical evaluation of patients with pruritus

1. Patient's clinical history: including hygiene habits that may dry the skin, contact with animals, occupation, leisure activities, infectious and parasitic diseases
2. Patient's history: allergies; renal, hepatic, hematologic, and psychiatric diseases
3. Family history of allergic and systemic diseases
4. Use of topical and systemic drugs

Table 61.5 Medical history taking for the assessment of pruritus

1. Occurrence of progression of previous episodes
2. Onset of current symptoms (acute, progressive)
3. Period of the day when the disease worsens (day/night)
4. Triggering agents (baths, clothes, room temperature)
5. Sensation caused by pruritus (bite, burn)
6. Frequency (continuous, intermittent)
7. Location (localized, generalized)
8. Association with daily activities (interference, triggering)
9. Patient's perception about pruritus (the extent to which it affects quality of life)

Patient's clinical history: A detailed past and current medical history should be taken with the purpose of identifying symptoms of systemic diseases, and family history should be taken to identify factors that predispose to systemic diseases [85–90]. It is also important to investigate the use of drugs that may trigger pruritus, possible allergenic agents, infectious diseases such as scabies, parasitological diseases, patient's occupation and lifestyle, and personal and family history of atopy and other allergic diseases. Personal and family psychiatric history of the patient should also be investigated.

Some factors also should be considered in pruritus evaluation [85]. When several family members are affected, scabies or other parasites should be considered. The relationship between pruritus and special physical activities are suggestive of cholinergic pruritus. Pruritus provoked by skin cooling after bathing should prompt consideration of aquagenic pruritus and may be associated with polycythemia vera or myelodysplastic syndrome. Nocturnal generalized pruritus associated with chills, fatigue, tiredness, and "B" symptoms (weight loss, fever, and nocturnal sweating) raises the possibility of Hodgkin's disease.

Somatoform pruritus rarely disturbs sleep but most other pruritic diseases cause nocturnal wakening. Seasonal pruritus frequently presents as "winter itch," which may also be the manifestation of pruritus in the elderly due to xerosis cutis and asteatotic eczema (Table 61.4).

History of pruritus: A detailed evaluation of pruritus may lead to the differential diagnosis of this condition. It is important to investigate how disease onset occurred, the period of the day when the disease worsens, whether pruritus is intermittent or continuous, and the sensation that pruritus causes, as well as duration of symptoms, severity, location, relationship with daily activities, triggering factors, and patient's perception about the symptoms [85, 86] (Table 61.5).

Measurement of pruritus: Pruritus is a subjective symptom that can be fully assessed only by the individual suffering from this symptom. However, several methods of assessment and measurement of pruritus have been developed in order to enable a better investigation of both the etiology of pruritus and the results of therapeutic studies. Visual analog scales and measures of scratching activity have been used for this assessment. A questionnaire developed by Yosipovitch et al. [19] evaluates the intensity, affective, and sensory dimensions of pruritus and may be extremely useful for the measurement of pruritus in systemic diseases.

Patient physical examination involves the search for dermatologic lesions that characterize pruritic dermatosis, xeroderma, jaundice, weight loss, hematomas, and excoriations caused by scratching [85–87]. General physical examination also should include palpation of the liver, kidneys, spleen, and lymph nodes.

Laboratory tests: Complete blood count, platelet, ferritin, serum iron, fasting glucose, stool test, erythrocyte sedimentation rate, evaluation of renal, hepatic, thyroid, and parathyroid function, hepatitis B and C markers, anti-HIV, and qualitative urine test. Other tests, such as immunoelectrophoresis, may also be performed in cases of clinical suspicion of the disease [85, 86].

Imaging tests: Chest X-ray and full abdominal ultrasound. Other tests may be requested according to clinical suspicion or medical judgment [85].

Histopathologic tests may sometimes elucidate the diagnosis, but are not routinely performed [85].

Patients with generalized pruritus and normal test results should be periodically monitored because they may present with malignant disease or other systemic diseases later in life, with pruritus as the initial symptom. In some cases, such as in patients with skin lymphoma, pruritus may persist for many years before the onset of clinical and laboratory manifestations of the disease and the possibility of diagnosis.

Therapeutic Approach

Considering that pruritus has various causes, there is no standardized recommendation for treatment. Topical and systemic therapies should be individualized, taking into account age, previous diseases, current medications, allergies, pruritus severity, and impact on quality of life [88, 89]. According to recent studies, the therapy should also address both cutaneous and central mechanisms of pruritus (Fig. 61.1).

The first step in pruritus treatment is focused on the diagnosis of an underlying disease and on how to control it. Depending on the underlying cause, the appropriate therapy may vary considerably, including treatment for a specific dermatosis, nonexposure to contact allergens, discontinuation of a medication, treatment of systemic, neurologic, or psychiatric diseases, and even surgical treatments for removal of an underlying tumor [88, 89]. Pruritus caused, for example, by hyperthyroidism or cutaneous T-cell lymphoma resolves with an effective treatment for these diseases.

When the cause cannot be determined, knowing the characteristics of the pruritus, such as intense itching hours and triggering agents, is extremely important for the therapeutic approach [88]. We should keep in mind that, in some cases, there is no totally effective therapy for itch relief. Therefore, patient counseling on measures for relieving pruritus is essential. Xeroderma occurs in a great number of these patients and should
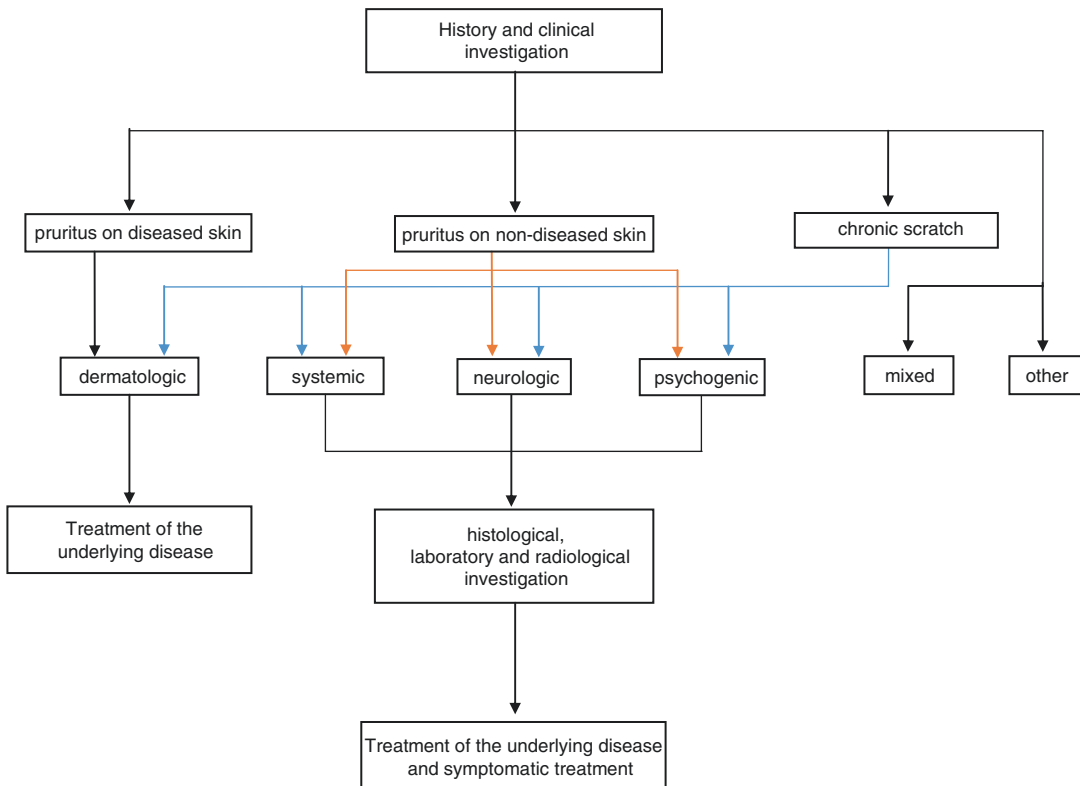
Fig. 61.1 Algorithm for the assessment of pruritus (Adapted from Weisshaar et al. [88])

always be addressed with the use of emollients. Being careful with active substances that may cause skin irritation and increase pruritus is also important. Itching causes traumatic skin lesions, which may be avoided by keeping fingernails trimmed. Elevated body temperature may increase pruritus. Measures such as wearing light clothes, staying in cooled areas, taking warm showers, and avoiding intake of alcohol and spicy foods help alleviate the symptom [88, 89]. It should be considered that chronic pruritus is often caused by several factors and may be intensified by many cofactors, suggesting a multifactorial origin [90].

Care of patients, particularly those with chronic pruritus, may often extend for a long time, with periods of diagnostic uncertainty, therapeutic failures, and psychological stress. Physicians should discuss treatment duration and diagnostic investigation with patients to increase adherence to treatment and establish a good doctor–patient relationship. In all cases, however, early treatment and patient counseling may prevent nerve sensitization and, thus, pruritus chronification.

Topical Treatment

Emollients: Topical emollients are the first-line therapy for mild or localized pruritus and for xeroderma. In hemodialysis patients with intense xeroderma, the use of emollients associated with other therapies is indicated [85]. These agents are likely to reduce pruritus by softening the sharp edges of the outermost layer of dry skin (stratum corneum) and by improving skin barrier function. In inflammatory diseases the skin barrier function is insufficient, and repetitive itching intensifies this problem, facilitating the entry of irritating substances. "Wet wrap" therapy may be useful and soothing in cases of extensive inflammation, such as in severe atopic dermatitis [91]. In this instance, the patient should first apply an emollient and a low-potency topical glucocorticoid on the affected area and then wear water-soaked cotton pajamas at night. This treatment should be limited to short periods (<1 week at a time) because of the associated risks of infection and absorption of topical glucocorticoids in excess. High pH solutions, such as alkaline soaps, may increase the secretion of serine proteases, which intensify itching and should be avoided in those patients. Conversely, moisturizers and skin care products with low pH (4.5–6.0) can be used [92].

Corticosteroids are not antipruritic agents, acting only in situations where the pruritus is caused by inflammatory skin reaction. In randomized clinical trials, moderate- to high-potency glucocorticoids have been proved to be an effective treatment for inflammatory skin diseases, such as atopic eczema, psoriasis, lichen planus, and genital lichen sclerosus et atrophicus [85]. High-potency glucocorticoids have also been used in medical practice in cutaneous manifestations secondary to chronic pruritus, such as prurigo nodularis and lichen simplex chronicus.

Capsaicin acts locally by desensitizing peripheral nerve fibers through depletion of substance P [93]. Usually its concentration varies from 0.025% to 0.075%. However, irritation on the injection site is a side effect, greatly limiting its utilization. Topical capsaicin is proven as an effective treatment for notalgia paresthetica and for hemodialysis patients with localized pruritus, as well as for patients with brachioradial pruritus [34, 79].

Menthol: Topical menthol relieves itching by activating cold-sensitive Aδ fibers, which are responsible for transmitting a cool sensation through the activation of a transient receptor potential cation channel subfamily M member 8 (TRPM8) [47]. Clinical experience has suggested that this substance may be effective in skin-care creams with concentrations varying from 1% to 5%, applied several times a day. Higher concentrations tend to cause skin irritation [94].

Calamine: Oil-based lotions and aqueous creams are effective in relieving pruritus. Patients often refuse to use it because of its pinkish color, and some formulations may cause skin dryness with water evaporation [3].

Topical anesthetics: Preparations such as pramoxine 1% or 2.5% cream and lidocaine 2.5% and prilocaine 2.5% cream were effective in alleviating neuropathic, facial, and anogenital pruritus in a number of cases. In a randomized clinical trial with chronic kidney disease-associated pruritus,

pramoxine 1% cream significantly reduced pruritus when compared with the isolated vehicle [95]. The long-term safety of these agents is still unknown.

Calcineurin inhibitors relieve itching in inflammatory diseases, such as psoriasis, eczema, seborrheic dermatitis, and anogenital pruritus [96]. However, a common adverse effect of these agents is a burning sensation that begins a few days after repeated application of the product.

Doxepin 5% cream, a tricyclic antidepressant with H1-receptor inhibitory properties, was effective in reducing the sensation of itching in patients with atopic eczema and contact dermatitis [97]. Potential adverse events include sleepiness and allergic contact dermatitis.

Systemic Treatment

Antihistamines: Sedating antihistamines, which are H1-receptor antagonists, are the most often used drugs in medical practice as a first-line therapy for pruritus, despite the shortage of clinical trials proving their efficacy for pruritic diseases, with the exception of urticaria. The benefit observed in medical practice may result from the sedative action of these medications, which can help patients with sleeping problems and relieve the symptoms. Nonsedating histamine H1- and H2-receptor antagonists have limited efficacy in the treatment of chronic pruritus [85, 98]. Antihistamines have little effect on hemodialysis patients and patients with cholestatic disease [57, 61].

Neuroactive drugs: Structural analogs to the neurotransmitter γ-aminobutyric acid, such as gabapentin and pregabalin, are an effective treatment for some types of pruritus. In randomized clinical trials in patients with chronic kidney disease, low-dose gabapentin (100–300 mg administered three times a week) was effective in controlling pruritus when compared with placebo [99]. Case reports show that these drugs may also be used in the treatment of postherpetic neuralgia, brachioradial pruritus, and prurigo nodularis [86]. The most common adverse events are constipation, weight gain, sleepiness, ataxia, and blurred vision.

Opioid agonist-antagonists: In patients with chronic urticaria, atopic eczema, and cholestasis, μ-opioid antagonists (naltrexone, nalmefene, and naloxone) have shown antipruritic effects [100]. Naltrexone and naloxone were effective for resistant itching associated with uremia and cholestasis. In randomized controlled trials conducted in Japan, nalfurafine hydrochloride (a κ-opioid agonist) significantly reduced itching in hemodialysis patients with chronic kidney disease [101, 102]. However, some studies involving patients with chronic kidney disease have shown inconsistent results [103, 104]. According to reports, butorphanol, a μ-opioid antagonist and κ-opioid agonist administered via intravenous route and approved by Food and Drug Administration for migraine treatment, reduced intractable pruritus associated with non-Hodgkin lymphoma, cholestasis, and the use of opioids [105]. Initial adverse effects of these agents, such as nausea, loss of appetite, abdominal colic, diarrhea, and insomnia, limit their utilization.

Tricyclic antidepressants: Serotonin reuptake inhibitors (paroxetine, sertraline, fluvoxamine, and fluoxetine) have been used to reduce psychogenic pruritus and various types of generalized pruritus [106]. A double-blind study demonstrated the efficacy of sertraline (daily dose of 100 mg) for the treatment of cholestatic pruritus [107]. Studies have suggested that the antidepressant mirtazapine (daily dose of 15 mg) may relieve nocturnal itching related to some types of cancer [108]. In several cases of intractable pruritus related to cutaneous T-cell lymphoma, patients treated with a combination of low-dose mirtazapine and gabapentin or pregabalin showed improvement of symptoms [109]. Tricyclic antidepressants, such as amitriptyline, have also been used in the treatment of chronic pruritus (neuropathic and psychogenic forms, for example) [85]. Paroxetine, a selective serotonin reuptake inhibitor, seems to have positive effects in low doses (5–10 mg a day). However, these effects tend to decrease after 4–6 weeks of use [3]. Ondansetron, a serotonin receptor antagonist, has been used for controlling pruritus in patients with cholestasis and hemodialysis patients. Case reports have shown important benefits, while randomized controlled trials have not demonstrated the same relevance.

Sodium cromoglycate: A mast cell stabilizer that has effects on the improvement of pruritus in patients with Hodgkin's lymphoma [110].

Rifampicin is indicated for the treatment of severe pruritus in patients with primary biliary cirrhosis and patients with cholestasis. Recent reports of drug-induced hepatitis caused by this medication reduce its therapeutic indication [111].

Cholestyramine reduces the levels of bile salts through chelation in the intestinal lumen. It is indicated in the treatment of cholestatic pruritus, but does not work when there is bile duct obstruction. It may also be used in hemodialysis patients [112].

Activated charcoal has shown positive results in relieving pruritus in hemodialysis patients with pruritus, at a daily dose of 6 g [112].

Thalidomide it is used for pruritus treatment in several pruritic diseases, such as eczema, psoriasis, senile pruritus, and liver diseases, and has an effect on hemodialysis patients, who have shown an improvement of more than 50% [113, 114].

Phototherapy: Observational studies have suggested that narrow-band UVB (NB-UVB) phototherapy, either isolated or in combination with ultraviolet A (UVA) radiation, reduces pruritus caused by chronic kidney disease and alleviates itching in diseases such as psoriasis, atopic eczema, and cutaneous T-cell lymphoma [115, 116]. In a randomized clinical trial involving patients with refractory itch secondary to chronic kidney disease [117], there was no significant difference in terms of efficacy between NB-UVB radiation and UVA radiation.

Liver transplantation and kidney transplantation: Both are indicated in patients with extremely serious pruritus who do not respond to any therapeutic modality [112].

Psychotherapeutic treatments may be used in cases of psychogenic pruritus. Some patients with pruritus that is difficult to control have depressive symptoms and may also benefit from psychotherapeutic treatment.

Glossary

Amyelinic C fibers One of three classes of nerve fiber in the central nervous system and peripheral nervous system. There are a myriad of mediators capable of stimulating these afferent nerves leading to itch, including biogenic amines, proteases, cytokines, and peptides. Some of these mediators can also evoke sensations of pain, and the sensory processing underlying both sensations overlaps in complex ways.

Capsaicin An active component of chili peppers, which are plants belonging to the genus *Capsicum*. Capsaicin is used to help relieve a certain type of pain known as neuralgia.

JAK2V617 mutation The *JAK2*V617 mutated allele is present in virtually all patients with polycythemia vera (PV) and in about 60% of those with essential thrombocythemia (ET) and primary myelofibrosis (PMF), which are the other two main clinical entities included within the group of myeloproliferative neoplasms. The presence of the mutation, and/or the burden of *JAK2*V617 allele, has been found to correlate with defined laboratory abnormalities and clinical features in the different myeloproliferative neoplasms.

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Prurigo

62

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Key Points
- Establishment of prurigo nomenclature and its differential diagnoses
- Presentation of the probable etiologies of chronic prurigo by showing the importance of the patient's clinical assessment
- Update of the therapeutic options for prurigo management

Concepts

The word *prurigo* has been used to designate a heterogeneous group of dermatoses that have papular eruption and pruritus as common aspects. Prurigo can be seen as a reactive clinical pattern, and 20% of the cases are still regarded as idiopathic. This term has been used whether the cause is known or unknown.

The clinical aspect of the lesions may vary and includes papules and nodules with excoriation, erosion, lichenification, crust-covered papules, and seropapules. Scars and residual hyperchromia can be found.

Clinical Presentation

The different types of prurigo had been described and designated by eponyms, with a confusing terminology. Greither [1] and Jorizzo et al. [2] classified the previously reported groups into acute, subacute, and chronic, as shown in Box 62.1. In addition to this division, we may include other varieties of prurigo in the classification, such as the prurigo of pregnancy, prurigo pigmentosa, and actinic prurigo [3, 4].

Box 62.1 Classification of Prurigo and Synonyms

Acute prurigo	Strophulus, prurigo mitis, papular urticaria, prurigo Hebra (prurigo "ferox"), prurigo simplex acuta Brocq, prurigo temporanea Tommasoli
Subacute prurigo	Prurigo subacuta Kogoj, prurigo vulgaris Darier, prurigo multiforme Lutz, lichen urticatus Vidal, prurigo simplex subacuta, urticaria papulosa chronica perstans, neurotic excoriation
Chronic prurigo	Prurigo nodularis Hyde, keratosis verrucosa, lichen obtusus corneus, urticaria perstans verrucosa, eczema verrucocallosum

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Other	Besnier's prurigo
	Prurigo of pregnancy
	Dermographic prurigo
	Prurigo pigmentosa
	Actinic prurigo
	Hutchinson prurigo

Adapted from Wallengren [3] and González et al. [4]

Acute Prurigo

Most often found in childhood, 86% of cases occur during the first 3 years of life. It is common among the economically lower classes, especially during summer [4].

Acute Prurigo: Simplex

Also known as strophulus, prurigo mitis, lichen urticatus, and papular urticaria, acute prurigo (simplex) is characterized by papules, vesicles, and/or urticaria during the early years of life, lasting for about a week. Hypersensitivity to arthropod bites, such as mosquitoes, ants, and fleas, is the main cause. Association with food allergies and psychological and infectious factors have also been described [5, 6]. Patients with acute prurigo show greater sensitivity to insect antigens during skin tests. Patient improvement in adulthood may correspond to desensitization resulting from repetitive bites [4]. On superficial blood vessels, granular deposits of C1q, C3, and immunoglobulin M were found, suggesting that dissemination is mediated by the immune complex [7].

It has sudden onset, with a small pruriginous vesicle/papule, which breaks up if scratched, being covered by a crust. It is believed that the early lesions primarily result from insect bites and that the subsequent symmetric and disseminated lesions are probably due to hematogenic dissemination of the bite-inoculated antigen [4].

Erosions, lichenification, and secondary infection may also be noticed. Lesions may show themselves as erythematous-edematous plaques, vesicles, and blisters, with blisters more often seen on the limbs. The papules persist over a week, with the development of new, nonconflu-
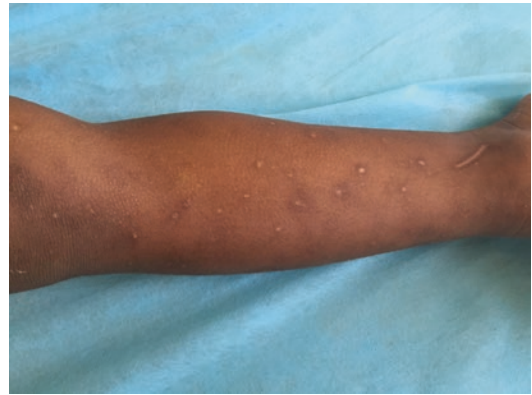
Fig. 62.1 Residual hypochromia surrounded by hyperpigmentation on a lower limb of a patient with strophulus

ent lesions; lesions of varying stages may coexist, sometimes leaving scars, hyperchromia, or residual hypochromia as seen in Fig. 62.1. The trunk and the limbs are the main locations; lesions are seldom seen on the face. The genital, perineal, and axillary regions are usually spared [4]. It is more frequently seen in children of 2–7 years of age, also being associated with the presence of atopy [3, 8].

The histopathologic examination is unspecific and shows the presence of perivascular inflammatory infiltrate, with lymphocytes and eosinophils, acanthosis, spongiosis with intraepidermal vesicle, and parakeratosis.

The diagnosis is clinical, based on lesion and pruritus history, location, and aspect. Epicutaneous tests can be helpful.

The differential diagnoses may include scabies, body pediculosis, herpetiform dermatitis, varicella, and urticaria.

Acute Prurigo: Simplex: Adulthood

Prurigo simplex temporanea Tommasoli has a presentation similar to that of strophulus, except that it occurs in young adults. The clinical presentation is characterized by papules on the extensor surfaces of the upper limbs and the anterolateral surfaces of the lower limbs. It has an insect-bite hypersensitivity, but may be related to hormonal factors, and infectious and parasite foci. In persistent lesions, systemic causes, such as diabetes, hepatopathies, nephropathies, and neoplasms,

must be assessed. The diagnosis is clinical, and the differential diagnosis includes herpetiform dermatitis and scabies [1, 2].

Prurigo Hebra

Known as prurigo "ferox", it displays pruriginous, eczematous, impetiginous, and lichenified papules, with lymphadenopathy mainly in atopic children. It occurs mainly in geographic areas lacking sanitation and good nutritional conditions [3]. The histopathology is the same as described for prurigo simplex.

Subacute Prurigo

Prurigo subacuta Kogoj, prurigo vulgaris Darier, prurigo multiforme Lutz, lichen urticatus Vidal, urticaria papulosa chronica perstans, and neurotic excoriations are multiple entities that share the same clinical and histologic presentation. It mainly affects middle-aged women, being related to emotional and psychogenic factors. Atopy, dermographism, and seborrheic dermatitis are also associated [9].

Subacute prurigo shows papules, excoriations, and symmetric urticariform plaques on the trunk, extensor surfaces of the limbs, face, and scalp, but not on the palms and the foot plantar region, as seen in Fig. 62.2. The pruritus develops in successive flares, and may be precipitated by exercise, heat, or emotional status [4].

Fig. 62.2 Subacute prurigo: papules, excoriation on the back of a male patient

The differential diagnosis includes herpetiform dermatitis, transient and persistent acantholytic dermatitis, and scabies.

The histologic examination shows acanthosis, hyperkeratosis, proliferation of nervous fibers, focal spongiosis, and perivascular and perifollicular inflammatory infiltrate.

Chronic Prurigo

Chronic prurigo includes prurigo nodularis, keratosis verrucosa, lichen obtusus corneus, and urticaria perstans verrucosa.

Prurigo Nodularis

Prurigo nodularis is the most characteristic representative of chronic prurigo in the terminology, described in 1909 by Hyde as nodules on the extensor surface of a woman's arms and legs, relatively rare and difficult to treat. Similar cases were reported by Hardaway in 1880 [10] and Brocq in 1900 [11]. In 1934, Pautrier showed the presence of dermal neural hyperplasia, known as Pautrier's neuroma [12].

Lichen simplex chronicus and lichen amyloidosis may correspond to the same disease spectrum given their similar clinical presentation and histopathologic findings, according to Weyers in 1995 [13]. Many authors regard prurigo nodularis as an atypical form of circumscribed dermatitis [14]; nevertheless, the indirect immunofluorescence of nerve bundles in prurigo nodularis showed increased immunoreactivity for substance P and the calcitonin gene-related peptide (CGRP) [15].

Prurigo nodularis shows symmetric, hardened, hyperkeratous, very pruriginous nodules and papules mainly on the extensor surfaces of the limbs, more often found in middle-aged women (Fig. 62.3). The lesions may show variation in quantity, and may affect the sacral region in 50% of patients and the abdominal region in 44%; palms, soles, and face are rarely affected [16]. Lesion onset is insidious, with chronic evolution. The pruritus is intense and intermittent, relieved by scratching to the point of skin mutilation and bleeding. In chronic lesions
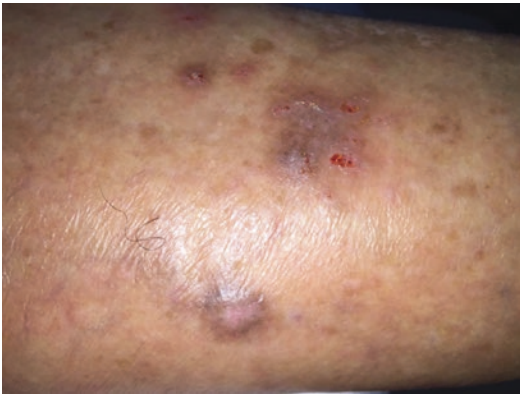
Fig. 62.3 Prurigo nodularis: pruriginous nodules and excoriations on the extensor face of the lower limb of a female patient

verrucous papules, lichenoid plaques, and excoriation may be noticed, as well as postinflammatory hyperchromia and scars. The papular distribution mainly follows the cleavage lines but not Blaschko lines [17].

The cause is unknown, although emotional factors may be present, and 65–80% of the patients are atopic [16]. Metabolic changes (such as anemia, hepatopathies, uremia, and myxedema), trauma, and neuronal etiology were suggested as related to prurigo nodularis [2, 16]. Focal causes of pruritus, such as insect bites, venous stasis, folliculitis, and nummular eczema are also related to this condition. Gluten-driven enteropathy with prurigo nodularis was already described by some authors, with improvement of both presentations when food is restricted [18–22].

Histopathology shows acanthosis, hyperkeratosis with proliferation of small vessels, and unspecific inflammatory infiltrate on the dermis (histiocytes, lymphocytes, mastocytes, and eosinophils). Fibroblast proliferation occurs, possible findings including a subepidermal fibrin deposit [2, 23, 24], papillomatosis, and irregular epidermal proliferation. The histologic findings may be similar to those of chronic eczema or persistent reaction to insect bite [16, 23]. Some authors believe the detected neural and vascular hyperplasia may result from mechanical trauma [25].

The diagnosis is clinical, according to the lesion history, location, and clinical aspect. Histologic examination may complement the diagnosis.

The differential diagnosis includes lichen simplex chronicus, hypertrophic lichen planus, pemphigoid nodularis, pruriginous epidermolysis bullosa, multiple keratoacanthoma, epidermal cysts, disseminated cutaneous cytomegalovirus in HIV-positive patients, and botryomycosis [26].

Endogenous and Exogenous Factors Related to Prurigo

Box 62.2 shows the main factors related to prurigo onset [3].

Box 62.2 Endogenous and Exogenous Factors Related to Prurigo

Endogenous	Exogenous
Atopy	Infections and parasitoses
Internal diseases	Contact allergy and drug reactions
Malabsorption	Light eruption
Malignancy	
Emotional factors	
Pregnancy	
Ethnic predisposition	
Adapted from Wallengren [3]	

Atopy
The term Besnier's prurigo is used to designate the chronic papular and lichenified form of atopic dermatitis as seen in Fig. 62.4. Many cases of Hebra prurigo have possibly involved patients living under poor social conditions. This pruriginous form of atopic dermatitis is less frequent and found in 9% of young adults who have had the disease during childhood [27].

Internal Diseases
Many internal diseases associated with pruritus may yield skin lesions that simulate prurigo nodularis resulting from scratching. Pruritus is a very common symptom in patients suffering from chronic renal failure who undergo hemodialysis. Perforating folliculitis with overlaying nodular prurigo has been described [28].

Fig. 62.4 Lichenified papules on the back of an atopic dermatitis patient

Diabetes mellitus, disseminated lupus erythematosus, systemic scleroderma, and deficiency of α1-antitrypsin may be associated with prurigo nodularis or prurigo-like lesions [29, 30].

Malabsorption

The association of prurigo nodularis with malabsorption was described in 1962 in a patient with celiac disease. Some other cases have been described since then in association with therapy-resistant enteropathies and prurigo nodularis. After some months of gluten-free diet, complemented with vitamins and iron, the intestinal symptoms improved and the skin lesions reduced or disappeared [31]. Anorexia nervosa and prurigo were associated because pruritus is one of the characteristics resulting from low weight. Once the weight is normalized, the prurigo lesions improve [32].

Malignancy

Pruritus and excoriations may be a nonspecific marker of internal malignant disease. Prurigo has been associated with T cell lymphoma and esophageal visceral, ventricular, rectal, hepatic, and biliary duct neoplasia. In a patient with lymphoma, the prurigo may appear before the symptoms of malignancy [33]. Prurigo may also be a warning sign for malignant change in patients with early tumors diagnosed as benign. In malignant cases prurigo nodules possibly result from scratching [34].

Emotional Factors

In clinical studies of patients with nodular prurigo, 50% of the subjects showed depression, anxiety, or some other psychological disease, and 72% of the patients reported that psychological problems were relevant to the skin disease [16].

Prurigo of Pregnancy

Prurigo of pregnancy, prurigo gestationis Besnier, is a pregnancy-specific, benign, self-limited dermatosis that affects 1 out of 300 pregnant women [35–43]. Earlier classified as pregnancy dermatosis of exclusion, it has now been reclassified as a subtype of atopic gestational eruption [43]. There are no risks for either the baby or the mother. Box 62.3 reports a related case.

> **Box 62.3 Case Report: Prurigo of Pregnancy**
> In 2010, Fan Wen-Ge and Qu Yun reported a case of a pregnant woman with a clinical presentation compatible with prurigo of pregnancy which, in 1995, resulted in fetal death. At that time the woman and baby underwent investigation whereby both showed no laboratory or chromosomal alterations, anomalies, or illnesses. In 2005 the same woman presented with gestational prurigo, underwent follow-up, and was treated with topical and intravenous corticosteroids to aid the baby's lung maturation; the gestational process was interrupted in the 34th week, with both being healthy [37].

It is considered the second most common gestational-specific dermatosis, although its etiology is unknown [41]. The trigger could involve some immunity-related change resulting from the pregnant condition: a decrease in cellular immunity and T-helper 1 (Th1) cytokine production compared with an increase in Th2 cytokine production through humoral immunity [36]. There seems to be a correlation with atopy, and some authors believe that it is the severe gestational pruritus in atopic patients [40–42]. Small 0.5- to 1-cm papules, extremely pruriginous, erythematous, and even hyperchromic, which evolve into nodules on the extensor surface of

the limbs may be noticed. Eventually they may spread; they usually appear as excoriated lesions more often occurring between the 25th and the 30th gestational weeks, although they are not limited to the period between those 2 weeks. The condition subsides some weeks postpartum, or may last for up to 3 months [42]. No vesicles or bullae are noticed [41].

Considered an exclusion diagnosis, it is based on clinical and normal laboratory tests, except for a possible increased IgE [36, 39–41]. The anatomopathologic examination is unspecific; it may present a perivascular lymphocytic infiltrate on the upper dermis, possibly affecting the epidermis. Direct and indirect immunofluorescence is negative.

Differential diagnoses are other gestational dermatoses, such as cholestasis and pruritic urticarial papules and plaques of pregnancy (PUPP), besides atopic dermatitis, arthropod bites, scabies, and drug reactions.

Ethnic Predisposition

Prurigo pigmentosa, or Nagashima's disease, is a rare condition in the Western world, more common in young Japanese women aged 23–27 years [44], although male cases and other ethnic background cases have been reported [45]. The etiopathogenesis remains uncertain. There are hypotheses of an association with ketosis, type 1 diabetes mellitus, anorexia nervosa, *Helicobacter pylori* infection, and atopy. It is not clear whether the highest incidence on Japanese women results from environmental factors or genetic predisposition [45]. It is severely manifested as intense pruriginous erythematous papules and papules/vesicles [45]. The lesions usually concentrate on the back, chest, and cervical region [46]. With evolution, the lesions heal and scars are seen as hyperchromic macules with a reticular pattern [45]. The clinical course oscillates, with both exacerbations and remissions [47].

The diagnosis is based on clinical and histopathologic manifestations. There is variation in the anatomopathology according to the stage of lesion evolution. The most recent lesions show a superficial perivascular neutrophilic infiltrate while the well-established lesions show spongio-

sis and many necrotic keratinocytes. Eventually, the late lesions display a predominantly lymphocytic infiltrate, with melanophages in the papillary dermis [45].

The differential diagnoses in the severe phase are herpetiform dermatitis, acute erythematous lupus, and linear IgA dermatosis; in regard to the remission phase, Ashy dermatosis, macular amyloidosis, and confluent and reticulated papillomatosis (Gougerot–Carteaud syndrome) must be excluded [45].

Infections and Parasitic Infections

The organ most affected by HIV is the skin [48]. An average 90% of HIV-positive patients will present some form of dermatosis during their lives [48–50]. The HIV pruritic-papular eruptions result in high morbidity and are difficult to treat [51]. It is a noninfectious chronic dermatosis, more often seen in highly immunologically affected patients [48, 52–54].

It is a chronic, recurrent condition with papular lesions, papulopustules, and/or nodules mainly affecting the distal region. There is intense pruritus and high recurrence. Eventually it disseminates [48]. Multiple lesions (more than 100) represent the usual pattern, although one or two lesions have been reported [50]. A linear disposition is common, usually evolving with dyschromias [50]. Both men and women are affected [50]. The etiopathogenesis is not well known and in HIV patients the treatment is challenging [53, 54]. Some authors believe there may be some hypersensitivity to arthropod bites [54, 55]. By virtue of the HIV there would be greater stimulus of B lymphocytes, inversion of the CD4/CD8 relationship, decrease in number and function of Langerhans cells, alteration of macrophage function, d IgE increase, possibly leading to a hypersensitivity reaction, more common in higher phototypes and CD4 cell count <50 [48, 50, 56]. Some research studies show lower levels of interleukin-2 and interferon-γ [54]. It is less often seen in Europe and North America [54, 55]. Firstly we must exclude causes leading to pruritus and, therefore, prurigo lesions. Also, infectious and neoplastic diseases such as lymphoma and hepatic, renal, and neurologic diseases must

be excluded. Eosinophilia and increased serum IgE may be found in laboratory tests [54, 57]. The anatomopathologic examination is usually unspecific; there is perivascular inflammatory infiltrate mainly comprising lymphocytes, with or without eosinophils. There must be hyperkeratosis, acanthosis, and papillomatosis with dermal fibrosis [50].

Differential diagnosis includes syphilis, drug eruption, scabies, folliculitis, demodicidosis, and tuberculids [54].

Strophulus prurigo may be caused by flea, mosquito, and tick bites. Lyme disease, mycobacteriosis, skin toxoplasmosis, and *H. pylori* infection have also showed an association with prurigo [3].

Contact Allergy and Drug Reactions

Contact allergy is usually related to intense itch, and can occur together with prurigo secondary to scratching. Patients with already established prurigo may develop a contact allergy to the drugs used to manage the condition. In a study at the Mayo Clinic, 29 out of 199 patients with prurigo who underwent contact tests were positive to neomycin, fragrance, and nickel. Many patients reported improvement after removal of the allergen [58].

Some drugs, such as etanercept, may induce acute prurigo; carbamazepine may induce subacute prurigo, and etretinate may induce nodular prurigo-like reactions [3].

Light Eruption

Actinic prurigo, also known as Hutchinson summer prurigo, is a photoinduced dermatosis, with the collaboration of hereditary and geographic components. It is more common among Native Americans and is seldom seen in Europe, Asia, and Oceania [59]. A possible relationship with the presence of HLA-DR4 has been investigated, and it is more frequent in higher-altitude inhabitants (1,000 m above sea level) [61]. Women are more affected than men [61], and actinic prurigo usually starts during childhood [62]. It may be induced by solar exposition, with higher incidence in the summer and spring, with possible remission in fall and winter [60]. Some authors have suggested that actinic prurigo may be a specter of polymorphous light eruption [63, 64].

The etiopathogenesis is unknown. Exposure to solar radiation has been suggested as the main trigger, which would yield the production of self-antigens and a consequent immune reaction in genetically predisposed individuals [59]. It manifests as flat papules, which may coalesce to create plaques and nodules in photoexposed areas, mainly the face, cervical region, upper torso, extensor aspect of the forearms, and dorsum of the hands. On the face the lesions tend to concentrate on areas of more direct incidence of light, such as the forehead, nasal dorsum, and malar regions. The lesions are heavily pruriginous, leading to the development of excoriations and possible scars. They are usually associated with cheilitis (mainly on the lower lip), conjunctivitis, and eyebrow alopecia [59, 60, 65].

The diagnosis is based on the clinical and histopathologic manifestations. Regarding the anatomopathology, the recent lesions usually show spongiosis while the older lesions are similar to prurigo nodularis [66]. The finding of HLA-DR4 favors the diagnosis. A photoprovocation test may be carried out [60]. Differential diagnoses include polymorphous light eruption, prurigo nodularis, cutaneous lupus erythematosus, and porphyria [60, 62].

Diagnosis

The diagnosis of prurigo is usually clinical. Additional investigation is important to define the related factors [67]. Box 62.4 synthesizes the basic assessment for prurigo when its cause cannot be established by early clinical assessment.

Box 62.4 Additional Examinations in Prurigo Investigation
- Complete blood count
- Urea, creatinine, and electrolytes
- Liver function
- Blood sugar
- Hepatitis serology

- HIV serology
- Total serum IgE
- Protein electrophoresis
- Thyroid/parathyroid function
- Chest X-ray or computed tomography/ magnetic resonance imaging
- Skin biopsy
- Patch test

Therapeutic Approach

When assessing a patient with a prurigo nodularis, it is important to search for the underlying cause. Acute prurigo also has inflammation and heavy pruritus that can be treated with topical corticosteroids and antihistamines. Subacute prurigo is a relapsing disease which demands treatment during its exacerbation periods. The courses of nodular and secondary prurigo are long. The chronic and persistent forms are treatment resistant, which force patients to go through many kinds of therapeutic experiences. Encouraging the patient to avoid scratching the lesions is important, since lesion manipulation worsens the symptoms [68].

Topical Treatments

The use of moisturizer must be encouraged because xerosis may exacerbate the pruritus [67].

Topical corticosteroids, preferably with occlusive membrane on the lesions, are very useful in acute and subacute injuries. In the case of more chronic lesions, the application of an intralesional corticosteroid is more effective. Coal tar with antipruritic and antibacterial properties is used during the severe phases in patients showing many excoriations. Calcipotriol is also effective for prurigo nodularis [69].

Cryotherapy has been recommended, since it induces thermal damage to peripheral sensory nerves. The application time varies from 10 to 30 s for two to four cycles. If postprocedural improvement of the lesion occurs, a topical corticosteroid must be applied. Intralesional lidocaine

and capsaicin cream are also effective. Menthol cream at 1% and camphor at 2% are good antipruritic applications [70–72].

Calcineurin inhibitors, such as pimecrolimus and tacrolimus, have been successful in decreasing pruritus in the investigated patients [73].

Systemic Treatments

Hydroxyzine (or similar sedative antihistamine of first generation) is very important for pruritus control, at 10–50 mg/day (or 0.5–1 mg/kg/day), every 6 or 12 h [3].

Systemic psoralen combined with ultraviolet A in research studies was effective, although it may lose efficacy after some time [74]. Narrowband ultraviolet B has also been proposed as an effective option [3].

Azathioprine 50 mg, twice a day, over 6–12 months, decreased pruritus and nodules in patients with prurigo nodularis. Relapses can occur between 2 months and 3 years after treatment interruption. Its efficacy in decreasing actinic prurigo symptoms has also been shown [75, 76].

Cyclosporine must to be used at high doses (3–4.5 mg/kg/day) over 6–9 months, resulting in pruritus decrease after 2 weeks. Pruritus and nodules may decrease and disappear during the period of treatment, although the condition relapses only 1 month after interruption [77].

Dapsone is the drug of choice to treat prurigo pigmentosa. Relapse occurs after treatment interruption. In Japan, minocycline 100–200 mg/day seemed to have anti-inflammatory action and provided a quick disappearance of pruritus, papules, and erythema; hyperchromia usually persists, being difficult to treat [44–46].

Naltrexone was successfully used to treat pruritus at a daily dose of 50 mg, with the possibility of doubling the dose in a few weeks. Naltrexone has a considerable antipruritic effect, thus playing a role in improving prurigo nodularis lesions [78].

Gabapentin and pregabalin inhibited neurotransmitters that provoke pruritus in prurigo nodularis patients [79, 80]. In a study with pregabalin, 23 out

of 30 patients (77%) showed complete remission of pruritus and prurigo lesions at a dose of 25 mg, three times a day, over 3 months. The maintenance dose is 50 mg/day for up to 2 years [80].

In 1973 the successful treatment of prurigo nodularis with thalidomide was described, since when it has been implemented [81]. Pruritus decreased in a few weeks while lesion involution took a few months. When there was drug interruption the pruritus took 2 months to reoccur and became severe in 4 months. The authors suggested a long-term treatment at a dose of 200 mg/day, possibly higher [82]. In patients with HIV prurigo, thalidomide has been signaled to have a promising role considering that it is not an immunosuppressive drug. However, one-third of the investigated patients developed peripheral neuropathy [51].

Thalidomide should not be used in women within fertility range if they do not use a satisfactory contraceptive method, because of the drug's teratogenicity.

Glossary

Erosion   Erosion is caused by loss of the surface of a skin lesion; it is a shallow moist or crusted lesion.

Excoriation   A scratch mark. It may be linear or a picked scratch (prurigo). Excoriations may occur in the absence of a primary dermatosis.

Lichenification   Lichenification is caused by chronic rubbing, which results in palpably thickened skin with increased skin markings and lichenoid scale. It occurs in chronic atopic eczema and lichen simplex.

Nodule   An enlargement of a papule in three dimensions (height, width, length). It is a solid lesion.

Papules   Small palpable lesions. The usual definition is that they are less than 0.5 cm diameter, although some authors allow up to 1.5 cm. They are raised above the skin surface, and may be solitary or multiple.

Plaques   A palpable flat lesion greater than 0.5 cm in diameter. Most plaques are elevated, but a plaque can also be a thickened area without being visibly raised above the skin

surface. They may have well-defined or ill-defined borders.

Vesicles   Small fluid-filled blisters less than 0.5 cm in diameter. They may be single or multiple.

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Urticaria

63

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Key Points
- Urticaria is a vascular pattern of response to immune and nonimmune stimulation of mast cells and basophils
- Based on the disease course, urticaria is classified as acute urticaria (less than 6 weeks since onset) or chronic urticaria (longer than 6 weeks of evolution)
- Urticaria can be induced by recognized stimuli, and in this clinical setting is called induced urticaria (e.g., water, cold, pressure, dermographism); in most cases there is no apparent cause and the urticaria is named spontaneous urticaria
- Nowadays, activation of the coagulation system has been demonstrated in at least 50% of patients with acute and chronic urticaria. D-dimer and F1+2 prothrombin fragment blood levels are directly related with the severity of the urticaria and/or angioedema in these patients
- The first step in the treatment of urticaria is the use of antihistamines per os. According to international consensus the new second-generation antihistamines must be used as a standard dose and in refractory cases to four-fold dose is recommended
- The second step in the treatment is add on to antihistamine treatment other drugs as omalizumab, cyclosporine or montelukast

Introduction

Acute urticaria (AU) and angioedema can be part of the clinical spectrum of anaphylaxis, and thus present a lethal risk if left untreated [1]. Chronic urticaria (CU) on the other hand is a disease with major negative impact on patients' daily activities and can therefore worsen their quality of life.

Over the past decade, European consensus has regulated the classification, diagnosis, and treatment of this group of diseases, based on critical analysis of evidence-based medicine [2].

This chapter approaches relevant aspects of the "Position Paper of the Fourth International Consensus Meeting on Urticaria, Urticaria

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2012," etiologic factors, and pathophysiologic mechanisms associated with CU in the literature that were deemed relevant in the new millennium [2]. Another important position paper about urticaria management was published by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology during 2014, and added relevant observation in urticaria study and practice [3].

Acute Urticaria

AU and angioedema are differentiated from CU practically on the basis of the duration of illness. The protagonist cell in both types of urticaria is the mast cells (Fig. 63.1) and basophils and their mediators (presynthesized, in their intracytoplasmic granules, or neosynthesized, such as leukotrienes, prostaglandins, and several types of cytokines) (Fig. 63.2a, b).

Urticaria and angioedema with duration of less than 6 weeks is termed AU [3]. If urticaria of less than 6 weeks' duration has features suggesting it might progress to CU, such patients should be periodically re-evaluated until a diagnosis is clarified [3].

AU and angioedema should be differentiated from anaphylaxis [3]. Urticaria/angioedema associated with signs and symptoms in organs other than the skin, such as the pulmonary tract (wheezing and cough), gastrointestinal system (vomiting and diarrhea), nervous system (dizziness and loss of consciousness), or cardiac system (changes in blood pressure or heart rate), can occur in patients with anaphylaxis [3]. Therefore, all patients who attend medical consultation showing wheals (Fig. 63.3a) and/or angioedema (Fig. 63.3b) must submit to a complete physical examination to detect extracutaneous signs, which can signal an anaphylaxis.

In many cases of AU, no specific cause is found [4]. Pite et al. [4] suggested that overall, success in identifying a cause in pediatric AU varies widely in the literature, from approximately 20% to 90%. This is mainly justified by different patient recruitment (e.g., from emergency departments, hospitalized or specialized units/departments), diagnostic testing performed, and criteria used for establishing a cause [4]. The possibility that a specific combination of several triggers is required to elicit AU could be one explanation for why symptoms may never reappear [4], and why most cases of AU do not remain as CU. Infections and drug and food hypersensitivity have been
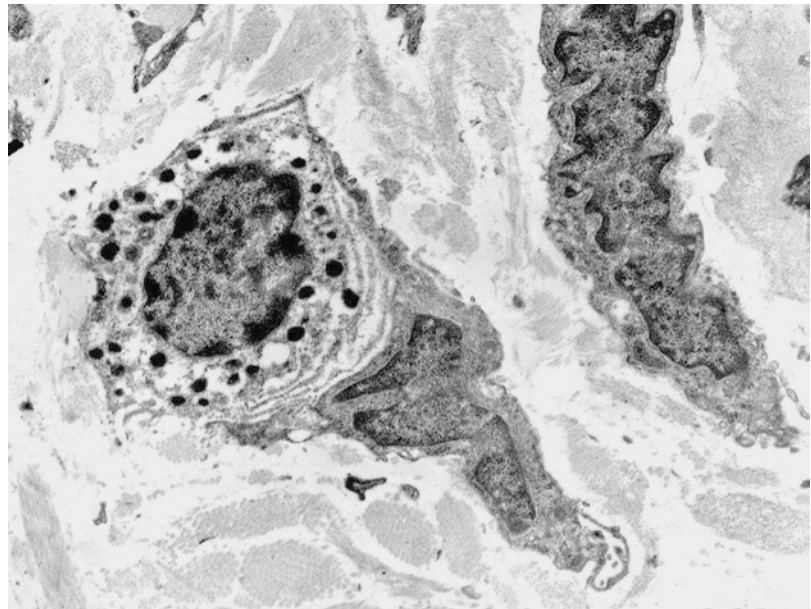
Fig. 63.1 Mast cell (*left*) and dermal dendrocyte (*right*) in acute drug-induced urticaria (electron microscopy, 25.000×).

reported as common potential triggers of AU in children [4]. In adults, AU often is trigged by infections or drug exposition [5].

Many etiologic factors or causes can be involved in AU [5]:

 (i) Idiopathic
 (ii) Viral agents (adenovirus, cytomegalovirus, enterovirus, Epstein–Barr virus, hepatitis A, B, or C, HIV, herpes simplex, influenza A, parvovirus B19, respiratory syncytial virus, rotavirus, varicella/zoster virus)
(iii) Bacterial pathogens (group A β-hemolytic streptococci, *Haemophilus influenzae*, *Staphylococcus aureus*)
(iv) Drugs: angiotensin-converting enzyme inhibitors (isolated angioedema), antibiotics (especially penicillin and cephalosporin), nonsteroidal anti-inflammatory drugs and acetylsalicylic acid, opiates, tramadol, paracetamol, dipyrone, proton pump inhibitors, isotretinoin, hyaluronidase, vaccination, etc.
 (v) Food (especially, protein antigens): cow's milk, egg, fish and seafood, fruit (peach, kiwi), tomato and other vegetables, wheat, yeast
(vi) Other conditions, substances, or parasites: *Anisakis simplex*, insect bites or stings, scabies in children, mycoplasma, Malaria, *Strongyloides*, *Ascaris*, latex, iodine radiocontrast, gadolinium-containing radiocontrast media, thyroid papillary carcinoma or other thyroid disease, sinus tract infection, urinary infection, systemic lupus erythematosus

During an attack of AU, wheals are variable in number and size [5]. More than 50% of the body
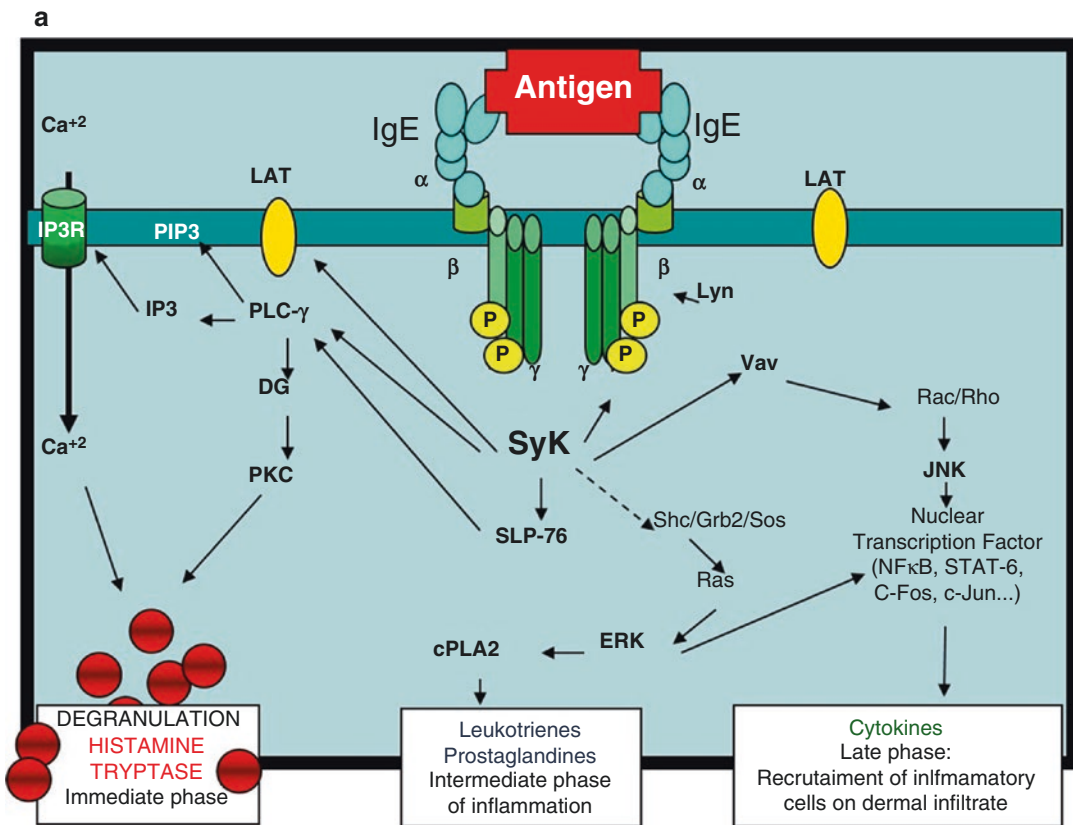
Fig. 63.2 (**a**) Mast cell mediators under anaphylactic degranulation (acute response) and neosynthesized mediators in late response to trigger stimulation. (**b**) Mast cell stimulation and preformed and neosynthesized mediators

b

Physical stimuli

Direct liberators (codein, 48/80 compound)

Endothelin

Protein A (Staphylococcus)

Proteins Fv (VHB, VHC)

C3a/C5a

Gp 120 (HIV)

IgE/Ag

Fcγ

FcγRI

FcεRI

FcγRI

PGE2

S C K F it

TNF

Neuropeptide (P substance neurotenesina, etc)

TLR2
TLR4
TLR7
TLR9

•**Neosynthesized Mediators:**
-Lipid derivates:
PGD_2, PGE_2, LTB_4, LTC_4, PAF
-Citokynes and Growth Factors:
GMC-SF, INFα, β, γ, ILα, IL1β, IL2
IL3, IL4, IL5, IL6, IL8, (CXCL8),
IL9, IL10, IL12, IL13, IL14, IL15,
IL16, IL17, IL18, IL22, LIF, M-CSF
IGF-1, NGF, PDGF, VEGF
-Chemokines
-NO, superoxide
-CRF, urocortin, p sunstance.

Late phase

PMN

EOS

LT

Mo

•**Preformed mediators:**
-Histamine
-Heparin
-Condroitin sulphate
-Tryptase
-Chymase
-Major Basic Protein
-Catepsina G
-Carboxypeptidase
•TNFα
•VEGF

Increased vessel wall permeability and Vasodilatation

Neural stimulation

Acute phase

Fig. 63.2 (continued)

surface area may be involved, and in one study the rash was described as generalized in 48% patients [5]. Urticarial wheals may occur alone or with angioedema [4, 5]. Coexistent angioedema has been reported in 16–31% of patients [5] but may be more common in children younger than 3 years (60%), who may also develop hemorrhagic wheals [5], suggesting a clinical setting of multiform urticaria or urticaria vasculitis. Systemic symptoms occur in up to a quarter of patients [5]. Wheezing, breathlessness, cough, rhinorrhea, dizziness, flushing, gastrointestinal upset (nausea, vomiting, diarrhea, or abdominal pain), headache, fever, tachycardia, joint pain, or conjunctivitis can occur with an attack of AU [5]. Rapid onset of such symptoms may indicate anaphylaxis [5].

Epinephrine should be prescribed if the diagnosis of anaphylaxis has not been excluded [3]. If the urticaria is part of an anaphylactic reaction, national guidelines and local protocols for anaphylaxis should be followed [54]. Intramuscular epinephrine, intravenous antihistamines, intravenous corticosteroids, oxygen therapy, salbutamol, fluid replacement, and other supportive treatment may be needed [5].

AU and angioedema are often but not always related to mast cell and basophil activation from multiple triggers, which include immunoglobulin (Ig) E–mediated and non-IgE-mediated mechanisms [3].

These cells play a broad critical role in the innate and acquired immune response because they express multiple receptors responding to specific antigens, as well as complement fragments, circulating immune complexes binding IgG and IgM, cytokines, changes in blood pressure, and immunologic activation [3].

Thus it is likely that mast cell activation in patients with AU and angioedema occurs through multiple pathways in addition to IgE [3]. The presence of a specific mast cell or basophil receptor for

proteases might account for IgE-independent acti-
vation of these cells through proteases in aeroal-
lergens, foods, and enzymes, as well as by
proteases generated by the complement response
to infectious agents [3].

AU and angioedema are more frequently asso-
ciated with identifiable conditions [3], as
described above [4]. When this disorder becomes
chronic, it is less likely to be associated with an
identifiable cause [1, 3].

Because AU and angioedema usually resolve
spontaneously, laboratory evaluation for chronic
illness is not required unless supported by the
clinical history or physical examination [1, 3].

Furthermore, empiric elimination diets (not
guided by history and testing) are not recom-
mended [3]. The presence of alimentary allergy
can be signaled if there is a direct correlation
among certain food protein ingestion and devel-
opment of signs including wheals and/or angio-
edema, wheezing, or gastrointestinal symptoms
after minutes or a few hours.

Although many cases of AU are caused by
viral or other infectious illnesses, extensive eval-
uation for specific viral pathogens or antiviral
therapy is not indicated unless suggested by the
clinical history [3]. For AU, skin testing or immu-
noassays to identify specific triggers for AU and

angioedema can be helpful if an allergic cause is suggested by history [3].

Skin testing in this scenario would usually be done after the resolution of AU and after suspension of antihistamines or through serologic testing in the presence of significant dermatographism [3]. Cutaneous biopsies might occasionally be useful for differentiating this condition from other inflammatory disorders [3] such as urticarial vasculitis.

Common causes of AU and angioedema, including medications and foods, should be identified by a detailed history and eliminated, if possible [3].

For the treatment of AU and angioedema, antihistamines are efficacious in most cases and recommended as first-line therapy [3]. Although first-generation antihistamines are rapidly acting and effective, in both pediatric and adult patients, they can be associated with sedation and impaired cognitive skills due to their ability to cross the blood–brain barrier, whereas these impairments are less evident or not evident with second-generation antihistamines as a class [3].

When agents that can cause drowsiness or impair performance are prescribed, adult patients and parents of child patients should be made aware of this potential side effect [3]. In patients with a poor response to antihistamines, a brief course of oral corticosteroids might also be required while attempting to eliminate suspected triggers and develop an effective treatment plan [3]. In our practice, we treat patients with AU under a scheme of prednisone or prednisolone 0.5–1 mg/kg/day for 7 days combined with at least 20–30 days of antihistamine use, after remission of signs and symptoms.

Chronic Urticaria

The duration of CU varies considerably [3]; however, physical urticaria tend to persist the longest, often for many years [3]. The prevalence of CU in the general population has been estimated to range from 0.5% to 5% [3]; however, the true point prevalence, cumulative prevalence, and lifetime prevalence of CU have not been established [3]. The incidence of CU has been estimated at 1.4% per year [3]. Some patients with CU might have both urticaria and angioedema, occurring simultaneously or separately [3].

Pathogenically, the skin mast cells are the most important cell in patients with CU, and histamine is the predominant mediator, although other cells and mediators also play a key role [3, 6]. A predominantly lymphocytic infiltrate can be found in the lesions of both patients with acute and those with chronic types of urticaria [3]. However, many patients demonstrate urticarial lesions that have a mixed cellular infiltrate: a mixture of lymphocytes, polymorphous nuclear cells (PMNs, such as eosinophils, neutrophils, basophils) [3], and other inflammatory cells, such as dermal dendrocytes [7].

Physiopathologic Mechanisms/ Etiologic Factors

Urticaria is a cutaneous reaction characterized by a sudden pruriginous rash accompanied by erythema and edema, and defined borders, location, size, and shapes that lasts for a few hours and is linked to the release of chemical mediators, mainly histamine, from mast cells in the dermis [1]. It is thus a heterogeneous group of diseases caused by or related to various factors, marked by the pattern of response with skin wheals and/or angioedema. According to its evolution over time, it can be classified as acute (<6 weeks) or chronic (>6 weeks) [2].

Several etiologic factors have been associated with CU throughout history: thyroid diseases, pseudoallergens, actual allergens, *Helicobacter pylori* infection, other infections/infestations, and autoimmunity/autoreactivity.

Helicobacter pylori **infection and its relation to CU** Hizal et al. demonstrated the positivity of autologous serum skin test (ASST) and high levels of IgG against *H. pylori* among patients with CU and concluded that the link between autoimmunity and infection by *H. pylori* warranted further studies [8].

Federman et al. [9], in an attempt to try and resolve this controversy, performed a literature

review and selected ten relevant studies published in English that fulfilled the following criteria: (i) patients with CU only, (ii) exclusion of other known causes of urticaria through specific tests, (iii) initial diagnosis of *H. pylori* infection established by serology, urea test, or endoscopy, and (iv) complete treatment of *H. pylori* with antibiotics [9]. The authors observed that the resolution of CU was more likely after the *H. pylori* treatment had been completed, than if the pathogen was not eradicated. About 50% of the population has serologic evidence of past or present *H. pylori* infections and at least 30% of CU patients are infected with this agent, but in general the treatment of this bacterium does not influence the course of CU [9].

Greaves [10] suggested that *H. pylori* infection might have an indirect role in CU pathogenesis. Because of the immunogenicity of the pathogen's cell envelope, it could be linked to the production of autoantibodies against Lewis X and Y blood group polysaccharide antigens, similar to that which occurs through molecular mimicry in *Campylobacter jejuni* infections and during Guillain–Barré syndrome. Therefore, *H. pylori* can have an indirect involvement in the etiology of CU by reducing the immune tolerance and inducing the formation of autoantibodies, including the production of autoantibodies to anti-FcεRIα [11].

Based on these data, there is still no overall consensus that the investigation of *H. pylori* should be performed as a routine or that when it is present the treatment might influence the course of CU.

Chronic Urticaria: Food as a Cause of Pseudoallergic Reactions

Tharp et al. [12] suggested that gastrin, a 17-amino-acid peptide released by G cells in the gastric antrum and proximal duodenum immediately after feeding, may be involved in anaphylactic reactions and urticaria reported after the ingestion of certain foods. This is corroborated by the observation that it is not always possible to establish a direct correlation between clinical symptoms and the detection

of antigen-specific IgE antibodies in cases of suspected food allergy [12].

In recurring CU, it is assumed that there might be histamine intolerance caused by an excessive dose of histamine in the diet and/or by abnormal histamine metabolism (diamine oxidase deficiency) [13]. Diamine oxidase is the main enzyme involved in the degradation of histamine, acting predominantly in the intestinal mucosa. Alcohol and some medications may decrease the activity of this enzyme and determine a higher sensitivity to histamine-rich or histamine-producing foods. Several experiments have demonstrated deficiency of diamine oxidase in enterocytes of patients with recurrent CU [13].

Certain fishes (tuna, sardines, anchovies), cheeses (Emmenthal, Gouda), salami, sausage, certain fruits and vegetables (tomatoes), wine, and beer are histamine-rich foods [14]. Drugs that may inhibit the intestinal activity of diamine oxidase and determine a higher concentration of histamine in general are imipenem, dobutamine, pancuronium, pentamidine, salazosulfapyridine, verapamil, isoniazid, clavulanic acid, dihydralazine, chloroquine, cycloserine, acetylcysteine, metoclopramide, and cefuroxime [14, 15].

Food additives such as preservatives, dyes, and natural salicylates may trigger or aggravate urticaria through pseudoallergic non-IgE-dependent mechanisms [6]. These additives are sodium metabisulfite, sodium benzoate, monosodium glutamate (MSG), sodium nitrate, tartrazine, erythrosine, sorbic acid, and butylated hydroxyanisole [15]. Regarding MSG, there is still no definitive conclusion about its causal relation to CU, despite the existence of controlled studies [16].

Di Lorenzo et al. [17] studied pseudo-food allergy in 838 patients with chronic/recurrent idiopathic urticaria and found it present in about 1.0–3.0% of their population. The provocation tests with a double-blind placebo-controlled technique were performed using the following substances: tartrazine (E102), erythrosine (E127), monosodium benzoate (E211), *p*-hydroxybenzoate (E218), metabisulfite (E223), and MSG (E620). The authors recommend considering the possibility of exclusion diets and provocation tests with food additives

in cases of CU/refractory angioedema that fail to fully respond to H1-antihistamine treatment. The general consensus is that, regarding CU, although food additives can aggravate the disease they are rarely its sole cause.

Dental Infections and Urticaria

The connection between dental infections and CU remains unclear [18]. There have been reports of transient urticaria with high fever outbreaks after dental treatment, suggesting that bacteremia and/or toxemia arising from treatment would induce urticaria through immune and nonimmune mechanisms. Histamine release by mast cells, secondary to lipopolysaccharides from oral flora Gram-negative bacteria such as *Veilonella* sp., could be relevant as a pathogenic factor in urticaria outbreaks in patients with odontogenic infection; furthermore, these anaphylotoxins can have an acute direct vasodilatory effect that determines urticaria outbreaks [18]. We believe that patients with urticaria should have their dental condition assessed.

Hepatitis B and C Infection

The fact that hepatitis B may be the cause of wheals or hives, particularly AU or CU, is already well established [19]. It has been widely debated that hepatitis C can cause hives. We concur with the opinion of Siddique et al. that patients with urticaria living in areas of high prevalence of hepatitis C infection should be screened for hives [20].

Helminthic Parasites and Infestations

The association of AU and angioedema or CU with infestations by parasites, protozoa, ectoparasites, and helminths has been postulated for many decades. In fact the literature is replete with case reports or case series, but there are few case–control studies or meta-analyses on this subject. The association of urticaria with the following parasites has been reported: *Giardia lamblia*, *Fasciola hepatica*, *Toxocaracanis*, *Echinococcus*

granulosus, *Strongyloides stercoralis*, *Hymenolepis nana*, *Blastocystis hominis*, *Ascaris lumbricoides*, *Anisakis simplex*, *Cimex lectularius* (bedbug), and *Argas reflexus* (bird tick) [21–30].

The association between parasitism and urticaria has been better established with *A. simplex* and recently with *B. hominis*. *A. simplex*, also known as *Pseudoterranova decipiens*, *Terranova decipiens*, or *Phocanema decipiens*, belongs to the Anisakidae family [31]. These nematodes have been described in infestations affecting humans after the ingestion of raw or not fully cooked seafood [31]. Anisakiasis is the term used to describe the acute form of the disease in humans. Seafood is the main source of larval infection. Aside from urticaria and anaphylaxis, other manifestations such as rheumatic symptoms, contact dermatitis, Crohn's disease, eosinophilic gastroenteritis, conjunctivitis, and asthma have been reported [31]. Sensitization to *A. simplex* can be investigated through specific RAST test in peripheral blood.

The prevalence of *B. hominis* ranges from 10% in developed countries to 50% in those in process of development [32]. Several authors have correlated different *B. hominis* genetic subtypes, especially subtype 3, with cases of CU and AU, a fact that not confirmed by other researchers [32]. Apparently the subtype identified may vary according to the different regions of the world, climate or seasonal changes, and source of infection [32]. Therefore, cases of CU in highly endemic geographic areas should be investigated for *B. hominis* in the stool and if the diagnosis is confirmed, treatment should be prescribed with metronidazole.

Chronic Urticaria and Thyroid

Hashimoto's thyroiditis and Graves' disease are associated with idiopathic CU [33, 34]. Antithyroid antibodies are found in 27% of patients with idiopathic CU and 19% of patients have abnormal thyroid function [35]. In such CU cases, high titers of antithyroid antibodies (antithyroglobulin and antiperoxidase) can be detected, whereas it occurs in only about 3–4% of the general population without thyroid diseases [36].
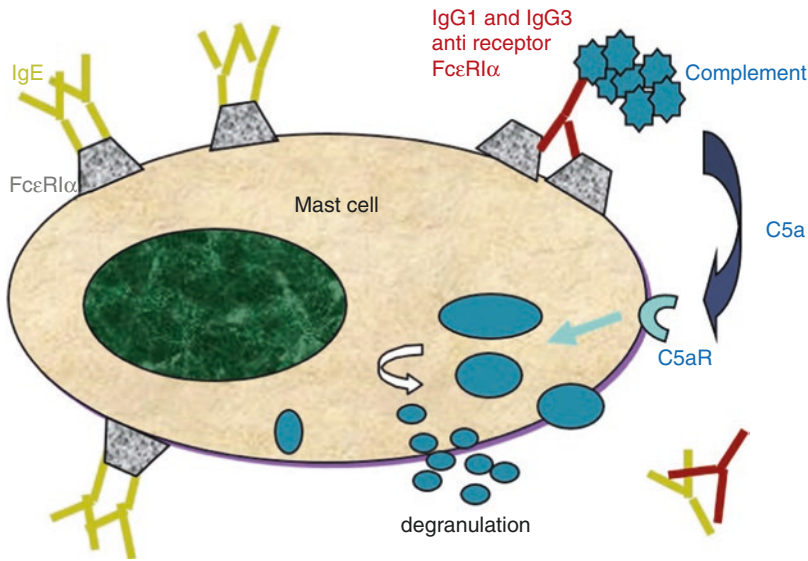
Fig. 63.4 Autoimmunity/autoreactivity in chronic spontaneous urticaria (CSU). Antibodies IgG1 and IgG3 are directed to high-affinity receptor for IgE in mast cells and basophils. After binding to receptor in membrane cell, this interaction stimulates an interaction among two IgE and antigen (allergen) and active intracellular pathways for degranulation and neoformation of lipid derivatives (leukotriene and prostaglandin) and cytokines. Besides this mechanism, some authors demonstrated the presence of IgE autodirected to circulating thyroid peroxidase antigens and double-stranded DNAs

The simultaneous occurrence of antithyroid antibodies and anti-FcεRIα in some patients with so-called idiopathic urticaria seems to indicate the existence of a disease or a "state" secondary to an underlying autoimmune process and/or a disruption of immune regulation. Rottem (2003) reinforces this concept, suggesting that there are no data to support a connection between the presence of antithyroid antibodies and CU pathogenesis, and that these are most likely parallel events, as occurs with autoimmune diseases [37]. In conclusion, tests for antithyroid antibodies and thyroid function should be performed in all CU cases in order to detect early those thyroid dysfunctions that require follow-up and treatment [37].

Autoimmune/Autoreactive Chronic Urticaria

About 50% of the cases of CU are considered autoimmune diseases, owing to the presence of circulating histamine-releasing autoantibodies, especially directed against IgE high-affinity receptors (FcεRIα) present in the cytoplasmic membrane of mast cells and basophils or anti-IgE autoantibodies (Fig. 63.4) [38].

There is clear evidence for a genetic predisposition to develop CU, i.e., there is a strong association between human leukocyte antigen (HLA)/familial inheritance and autoimmune etiology in some cases, especially those with a positive autologous serum skin test (ASST) [38]. There are reports suggesting a connection between CU with a positive ASST and autoimmune diseases, such as autoimmune thyroiditis, celiac disease, rheumatoid arthritis, Graves' disease, and type 1 diabetes mellitus, in addition to a higher frequency of autoimmunity serum markers such as rheumatoid factor, antinuclear antibody, and antithyroid antibody [33]. Patients with CU and positive ASST have a high frequency of HLA-DRB1*04 and its associated allele DQB1*0302 when compared with the healthy population and patients with CU and negative ASST [38–40].

Unfortunately, we still lack a routine laboratory test to detect anti-FcεRIα and/or circulating

and functionally active anti-IgE. ASST autoantibodies have been considered an in vivo test to confirm both the presence of these autoantibodies and histamine release in basophils [38, 40].

In a retrospective study performed in Israel, Confino-Cohen et al. [40] analyzed data from 12,778 patients with CU during a period of 17 years and compared clinical and laboratory data with 10,714 control patients without CU. There was a definite increase in the odds ratio of hypo- or hyperthyroidism and the presence of antithyroid antibodies among patients with CU. Female patients with CU had a higher incidence of rheumatoid arthritis, Sjögren's syndrome, celiac disease, type 1 diabetes mellitus, and systemic lupus erythematosus during their lifetime, and those illnesses were diagnosed mainly in the 10 years following the diagnosis of CU. Increases in mean platelet volume, and positivity for rheumatoid factor and antinuclear antibodies were more prevalent and significant among patients with CU [6, 40]. Probably the presence of a chronic inflammatory process, implied by the increased mean platelet volume, shares a common pathogenic pathway with autoantibody formation in patients with CU. However, 50–60% of CU cases remain idiopathic, the so-called spontaneous CU [2, 40].

Recently, some authors demonstrated the activation of the coagulation system in patients with CU via thrombin generation, initiated by the increased expression of coagulation tissue factor on eosinophils [41–43]. This determines a potential contribution to the increase in capillary permeability. These patients often have elevated coagulation and fibrinolysis serum markers, such as fragment 1+2 prothrombin and D-dimer, whose levels seem to correlate with the severity of CU [41–43]. In animal models, thrombin shows increased capillary permeability by direct action on the endothelium and indirectly by inducing the release of proinflammatory mediators by mast cells, increasing C5a in the absence of C3, and bypassing the first part of the complement cascade [41–43]. It is possible that a synergy between the action of autoantibodies and the coagulation cascade exists in some patients with CU [41].

An article defining and proposing criteria for the diagnosis of autoimmune urticaria, by the European Academy of Allergy and Clinical Immunology, was published in 2013 [44]. The following criteria were proposed as the gold standard for autoimmune CU [44]: (a) presence of a positive in vitro biological test to demonstrate the autoantibodies' functionality (basophil histamine release test or the expression of a basophil activation marker such as CD63 or, better still, CD203c during flow cytometry) AND (b) positive autoreactivity (positive ASST) in order to demonstrate the in vivo relevance of mast cell degranulation and the increase in capillary permeability, AND (c) a positive immunologic assay for autoantibodies against FcεRIα receptors (western blot or ELISA) to demonstrate the autoantibodies' specificity.

In daily practice, however, most physicians have only the autologous serum skin test available, and its positivity in a patient with CU can only suggest "autoreactivity" [6]. Unfortunately, in Brazil we do not yet have the other tests indicated for the diagnosis of autoimmune CU [6].

Chronic Urticaria and Allergic Etiology

The link between CU, IgE sensitization, aeroallergens, and allergy has been much discussed but seldom studied [45].

Between 2006 and 2008 in France, Augey et al. [45] studied 128 adult patients with CU under the aspects of IgE sensitization and allergy. These authors considered CU an allergic disease if: (i) there was a high correlation of positive prick tests (skin puncture tests) to an allergen that was clinically relevant in the patient's medical history, and (ii) a complete remission of urticaria occurred within the first 2 months after the allergen was removed. Among 105 patients with interpretable puncture tests, 46.7% were sensitized by IgE. Two patients had clinically relevant puncture tests; however, their CU had many other triggering factors and there was no remission after withdrawal from allergen exposure. The authors concluded that the rate of IgE

sensitization is higher among patients with CU compared with the general adult population [45]. However, these CU cases cannot be considered as an expression of IgE-mediated allergies, but as a chronic inflammatory disease that is more common in IgE-sensitized subjects and induced by many factors, among which IgE-mediated allergy is the least frequent [45].

The relevance of allergic sensitization to dust mites in the etiology and treatment of CU is still unknown. In Turkey, Caliskaner et al. [46] studied 259 patients with CU and angioedema, without respiratory allergic diseases (rhinitis and/or asthma) and compared their results with 300 healthy controls and 300 atopic patients. Immediate cutaneous reactivity to one or more allergens was detected in 71 cases of CU and angioedema (27.4%). The most commonly detected allergen was residential house dust (24.7%) [46]. Positive prick tests (skin puncture tests) were correlated with other aeroallergens, including pollen, mold, and cockroaches in 7.7%, 0.4%, and 0.8% of patients, respectively. In the healthy control group, 7% of cases were considered atopic regarding the prick test results [46]. Pollen (6%) and house dust (4.7%) were the most commonly found allergens in the healthy control group. In the atopic control group, pollen and dust mites were the allergens most commonly detected in the prick test (62% and 50.3%, respectively) [46]. The difference between patients with CU and the control group was statistically significant regarding the presence of atopy and sensitivity to mites ($p < 0.001$) [46]. The proportion of skin tests that were positive to house dust was higher in the CU group than among healthy cases, but not as high as in atopic patients [46]. Furthermore, the rate of cutaneous reactivity to other aeroallergens did not differ from the healthy group. The authors concluded that urticaria, as an isolated clinical manifestation in patients who are sensitive to dust, was not common in this study [6].

Therefore, it is well established that CU is not included in the indications for immunotherapy with allergy desensitization [46]. In our opinion, therefore, the systematic practice of skin prick test reading should not be routinely performed during the investigation of CU, unless there is a definite correlation between episodes of CU worsening and data from the patient's medical history.

Definition, Classification, and Course of the Disease

Urticaria is characterized by the sudden appearance of wheals, which may be accompanied by angioedema [47, 48]. Superficial dermal edema is called wheals or hives, while edema in the deep dermis, hypodermis, and gastrointestinal tract is known as angioedema [47, 49]. Diagnosis is mainly clinical [1].

Wheals have three typical features: (i) central edema of variable size, almost always surrounded by a reflex erythema, (ii) association with pruritus and sometimes a burning sensation, and (iii) ephemeral nature, with the skin returning to its regular appearance in usually 1–24 h. Angioedema is characterized by: (i) a sudden, pronounced edema of the deep dermis and subcutaneous tissue, (ii) pain more often than pruritus, (iii) frequent involvement of mucous membranes, and (iv) resolution of symptoms in about 72 h, more protracted than in the case of wheals [1].

It is well known that the spectrum of clinical manifestations of the different subtypes of urticaria is very broad. Moreover, two or more subtypes of urticaria can coexist in the same patient. During the Fourth International Consensus Meeting on Urticaria 2012, the adoption of a clinical classification (shown in Chart 63.1) was proposed [2].

Undoubtedly, this classification is not perfect since there are still some inconsistencies, e.g., physical urticaria also has a chronic nature [46]. However, physical urticarias are grouped as a result of the special nature of their causal factors, while in AU and CU, lesions appear spontaneously without external physical stimuli [3].

In 2001, Kozel et al. [47] published a study, conducted in the Netherlands, of 220 adults diagnosed with urticaria. Of these, 72 cases (33.2%) had physical urticaria, 24 (10.9%) had a combination of physical urticaria and idiopathic CU,

Chart 63.1 Classification and subtypes of urticaria

Type of urticaria	Duration
Spontaneous urticaria:	
1. Acute urticaria	1. Less than 6 weeks
2. Chronic urticaria	2. More than 6 weeks
Unknown etiology	
Induced urticaria:	
(i) Dermographism	(i) Application of mechanical forces to the skin (wheals appear in 1–5 min)
(ii) Delayed pressure urticaria	(ii) Vertical pressure (wheals appear after 3–8 h of latency)
(iii) Urticaria secondary to cold	(iii) Cold air/water/wind
(iv) Urticaria secondary to heat	(iv) Localized heat
(v) Solar urticaria	(v) Ultraviolet (UV) and or visible light
(vi) Urticaria/vibratory angioedema	(vi) Vibratory forces, usually pneumatic devices
(vii) Aquagenic urticaria	(vii) Contact with water, regardless of its temperature
(viii) Cholinergic urticaria	(viii) Stress, perception of body temperature elevation by the hypothalamus
(ix) Contact urticaria	(ix) Allergic or pseudoallergic

Adapted from Zuberbier et al. [2]

Chart 63.2 Urticaria Activity Score (UAS): daily evaluation during the most prominent number of lesions and intensity of itching

Score[a]	Wheals	Pruritus
0	Absence of wheals	Absence of symptoms
1	Light (<20 wheals/24 h)	Light
2	Moderate (21–50 wheals/24 h)	Moderate
3	Severe (>50 wheals/24 h or large confluent areas with wheals)	Intense

[a]Maximum score is 6 (3 points for number of wheals and 3 points for pruritus intensity)

and 78 (36%) had idiopathic CU; 20 cases (9.0%) were induced by drugs, 15 (6.8%) by food, four (1.8%) by infections, and 3 (1.4%) by internal diseases; and 2 (0.9%) were urticaria due to contact. Causality was established in 53.1% of the cases. Thirty-five percent of the cases were free of symptoms after 1 year and in 28.9% there was an improvement of symptoms. Spontaneous remission occurred in 47.4% of patients in whom no causal agent was identified and only in 16.4% of cases with physical urticaria. In this study, patients with physical urticaria had the worst prognosis regarding disease duration, as 84% of them still had symptoms after 1 year [47]. Another important factor in urticaria is to classify the intensity and activity of the disease. Młynek et al. [48] proposed a classification, later validated in 2008, which was easy to adhere to by both physicians and patients in their daily activities (Chart 63.2) [9].

Due to the variable intensity pattern of urticaria throughout the day, sequential dermatologic inspections (visualization of the skin) should be made periodically (Urticaria Activity Score (UAS) 0–6 points) to increase the accuracy of the score; the sum of points scored over 7 days (UAS 7, 0–42 points) is currently being used in clinical studies [48]. In general, larger wheals indicate outbreaks that are more intense and more difficult to treat [48].

Diagnosis

Spontaneous UC is a disease that causes a serious impact on patients along with high direct and indirect costs to the health system, as well as extensive socioeconomic implications, since it delays by about 20–30% the return of productive individuals to the work force [2]. Due to the wide heterogeneity of this group of diseases called urticaria, routine investigation should include a thorough history, extensive physical examination, quests for information on possible causal factors, and important data on the nature of urticaria [2]. The next step is laboratory testing to exclude significant systemic diseases, provided they are warranted by clinical history and physical examination [2].

Skin biopsy of wheals must be performed if there is suspicion of vasculitis or urticaria vasculitis, which usually persists for more than 24 h in the same location and can leave hyperchromic or purplish residual lesions, although this does not always occur [2, 6, 49]. Furthermore, burning symptoms isolated or coupled with pruritus may be reported by these

patients. Skin biopsy of wheals is also indicated in cases that are refractory to treatment with antihistamines [2, 49].

Considerations on Autologous Serum Skin Test

In 1946, Malmros published the first report on the likelihood of autologous serum (from patients with urticaria) triggering positive skin tests, although this hypothesis was disregarded for decades [50].

The ASST is an in vivo test that measures the autoreactivity of an individual [44, 51]. This autoreaction is characterized by the formation of wheals and pruritus in response to an intradermal injection of autologous serum (obtained from the patient during the clinical activity of urticaria, or crisis), which acts indirectly through the release of mediators from mast cells/other cells or directly by acting on the skin's microvasculature [44, 51]. It should be stressed that autoreactivity does not define, nor does it imply the presence of, autoimmune urticaria, but may be an indication of mast cell activation by the autoantibodies present in the autologous serum of patients with CU and positive ASST [44, 51].

The frequency of positive ASST in adults with CU ranges from 4.1% to 76.5% depending on different criteria for positivity, including confirmation by histamine release test (HRT) [44]. The discrepancy in results can be attributed to patient selection bias, severity of illness, methodology, and interpretation of the results or even the actual prevalence of autoimmune urticaria in the population tested [44]. The frequency of positive ASST is 45.5% (95% confidence interval (CI), 24.7–74.4%) when establishing a 1.5-mm difference in diameter between the response obtained with cases tested with saline (negative control) and 43.5% (95% CI, 34.8–62.1%) when the difference is 2 mm [46]. A positive ASST result on a CU case could mean an autoreactive CU [44].

Current recommendations to establish the methodologic standardization for ASST are summarized in Fig. 63.5 [44]. In order to perform an ASST it is necessary to take the patient off any medication with antihistamine activity for a variable period of time before testing, as depicted in Chart 63.3 [44].

Considerations on the Autologous Plasma Skin Test

The ASST is based on intradermal injection of autologous serum, and merely represents a diagnostic procedure used in autoimmune CU [52, 53]. The plasma used in the autologous plasma skin test (APST) also contains coagulation factors and sodium citrate. Therefore, the positivity occurring in the APST may be due both to autoantibodies that induce thrombin activity and/or to the sodium citrate [52].

In a study with 96 patients with CU, Asero et al. [53] found that 51 of 96 patients (53%) were ASST positive, and 61 of 71 (86%) were APST positive. Asero's group in Italy advocates that the APST increases the sensitivity of diagnosis in cases of autoreactive CU, since it indicates the activation of the coagulation cascade in the presence of autoantibodies. These autoantibodies, when degranulating mast cells and basophils, activate eosinophils, which in turn release tissue factor, thus stimulating the coagulation cascade and compensatory fibrinolysis. The latter will generate thrombin, which will induce the activation of more mast cells and the vascular endothelium; D-dimers are also detected at higher levels as a final result of fibrinolysis.

In another multicenter study [52], the positivity rate was 37.5% for ASST and 43% for APST among 200 patients with CU (146 women and 54 men).

Yildiz et al. [52] studied 42 patients (19 males, 23 females; mean age 35.7, range 28–76 years) and 35 healthy volunteers (19 males, 16 females; mean age 30.28, range 20–80 years). The authors performed APST, ASST, negative control with saline and sodium citrate, and positive control with histamine. In terms of positivity, no statistically significant difference between APST and ASST was found [52]. Therefore, the authors concluded that APST to assess autoreactivity in clinical practice was not superior to ASST, and

Fig. 63.5 Steps for
performing autologous
serum skin test (ASST)

AUTOLOGOUS SERUM SKIN TEST

1
- Collect blood in a sterile tube without preservatives
- Meticulously identify the tubes with the patient's name

2
- Let the blood coagulate at room temperature for 30 minutes
- Centrifugate the sample at 450-500g for 10 minutes

3
- Cleanse the anterior surface of the forearm with antiseptic, avoiding the wrist and the skin that presented wheals in the last 48 hours and space each of the 3 injections (autologous serum, positive control and negative control) 3 to 5 cm from each other
- Apply intradermal injections (sterile siringe with 27G needle) of: (i) 0.05 ml of saline solution as negative control, (ii) prick test with histamine 10mg/ml solution or intradermic injection of 0.05 ml histamine at 0.5 to 1μg as positive control and (iii) itradermic injection of 0.05 autologous undiluted serum

4
- Wait for 30 minutes

5
- Read the test by drawing on the margins of the wheals edma with a pen
- Confirm the occurrence of a positive reaction to histamine (positive control)

6
- Calculate the mean of the perpendicular diameters of any erythematous-edematous reaction to the autologous serum skin test and negative control (saline solution)
- Consider the test positive if: mean diameter of autologous serum wheal - mean diameter of saline solution wheal ≥1.5 mm

further studies should be conducted to corroborate these findings [6].

Treatment

The treatment of urticaria includes pharmacologic and nonpharmacologic interventions [55, 56]. Nonpharmacologic interventions for phys-ical urticaria are limited to reduction of stress levels and sun exposure, and diminished alcohol intake. There is little evidence that reducing drug intake and exposure to pseudoallergens would improve urticaria in these patients, except in cases of spontaneous CU, which is aggravated by nonsteroidal anti-inflammatory drugs (especially aspirin) in 25–30% of patients with urticaria [55]. Cooling lotions, such as 1%

Chart 63.3 Different antihistamines and time of dropout to perform the autologous serum skin test

Drug/daily dose	Elimination T$_{1/2}$ (h)	Length of suppression of urticarial response secondary to histamine prick test	
		Single dose (h)	Continuous use (days)
Acrivastine 8 mg	1.4–3.1	8	UD
Azelastine	22	12	7
Cetirizine 10 mg	7–11	≥24	3
Cyproheptadine 8 mg	UD	UD	11
Dexchlorpheniramine 4 mg	UD	UD	4
Diphenhydramine	9.2 ± 2.5	UD	UD
Ebastine 10 mg	10.3 ± 19.3	≥24	3
Fexofenadine 60 mg	14.4	24	2[a]
Hydroxyzine 0.7 mg/kg	20 ± 4.1	26	UD
Loratadine 10 mg	7.8 ± 4.2	24	7
Mizolastine 10 mg	12.9	24	UD
Levocetirizine 5 mg	7 ± 1.5	UD	4
Desloratadine 5 mg	27	UD	UD
Doxepin 25 mg	17	4–6 (days)	UD

UD unavailable data

[a]Similar length of suppression with 120 or 180 mg
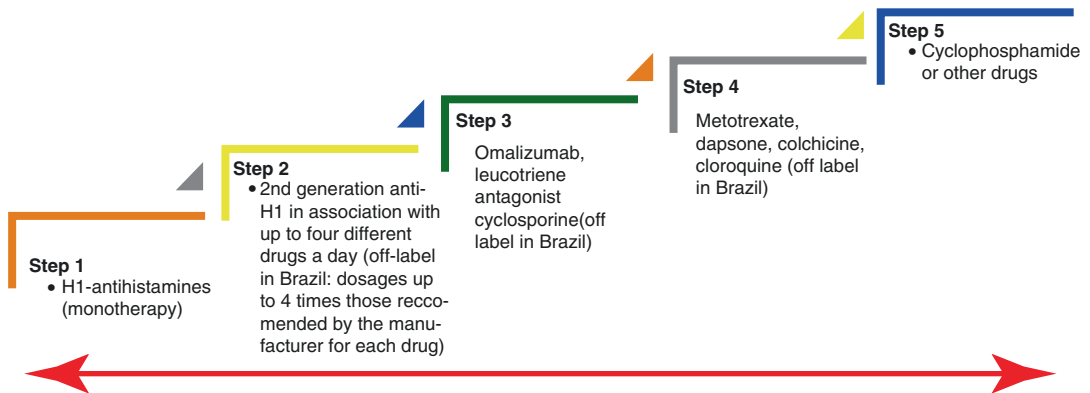
Fig. 63.6 Treatment schedule proposed for chronic spontaneous urticaria patients in Brazil

Step 1
• H1-antihistamines (monotherapy)

Step 2
• 2nd generation anti-H1 in association with up to four different drugs a day (off-label in Brazil: dosages up to 4 times those reccomended by the manufacturer for each drug)

Step 3
Omalizumab, leucotriene antagonist cyclosporine(off label in Brazil)

Step 4
Metotrexate, dapsone, colchicine, cloroquine (off label in Brazil)

Step 5
• Cyclophosphamide or other drugs

menthol, can be useful to many patients with very active urticaria [55].

In our opinion, it is important in the treatment of CU to make the patient understand the need for continuous, and not intermittent treatment, in order to achieve the proper control of the disease; and also to explain that this is a chronic condition that requires uninterrupted medication similarly to hypothyroidism or diabetes mellitus, although unlike these two diseases urticaria tends to go into remission over time [6].

Treatment of wheals outbreaks is sequential or made in steps, but its main cornerstone is the use of antihistamines (Fig. 63.6) [55]. Therefore, H1

antihistamines (anti-H1) are crucial in the treatment of urticaria [55, 56]. Nevertheless, some CU cases may present a marked inflammatory cell infiltration, which can be somewhat refractory to anti-H1 and respond satisfactorily to oral corticosteroids or second-line agents (montelukast, dapsone, or colchicine) [55–57].

Criado et al. [58] studied 22 CU patients unresponsive to conventional antihistamine treatment. The patients had uncontrolled urticaria even with multiple combinations of antihistamines at maximum doses and corticosteroids for short cycles (prednisone 20–40 mg, orally, once a day, 3–7 days per month). Cutaneous biopsies of the

wheals were performed. The findings were classified as: (i) dermal perivascular mixed inflammatory infiltrate composed of lymphocytes, monocytes, and neutrophils and/or eosinophils; (ii) inflammatory infiltrate formed mainly by neutrophils; and (iii) inflammatory infiltrate composed mainly of eosinophils. According to histopathologic results, patients were subjected to one of the following regimens: class A, antihistamine associated with dapsone; class B, colchicine or dapsone; class C, montelukast. Four patients in class A, eight in class B, and seven in class C showed complete remission of urticaria after 12 weeks of treatment; one patient in class B and two in class C did not respond to therapy. Two years after treatment discontinuation, 16 patients remained urticaria free. The authors concluded that dapsone or colchicine might be effective adjuvant drugs in the presence of intense neutrophilic infiltrate, as could montelukast in cases with eosinophilic infiltrate [58].

H1-antihistamines have been used in the treatment of urticaria since 1950 [59]. Although first-generation drugs have a relatively lower cost than second-generation ones, the former have pronounced anticholinergic effects, with sedative action on the central nervous system (CNS) that lasts 12 h, while their antipruritic effects last between 4 and 6 h [59]. As a consequence, there have been many reports on interactions between first-generation anti-H1 drugs, alcohol, and medications (analgesics, hypnotics, sedatives, and antidepressant drugs) that cause unwanted effects in the CNS [59, 60]. In addition, monoamine oxidase inhibitors may prolong and intensify the anticholinergic effects of first-generation H1-antihistamines [59].

The most used first-generation, anti-H1 drugs to treat CU belong to the groups of ethanolamines (diphenhydramine, clemastine), piperazines (hydroxyzine, dexchlorpheniramine), and piperidines (cyproheptadine and ketotifen) [59]. Some randomized studies compared the effects of cetirizine versus hydroxyzine and loratadine in the treatment of CU and demonstrated similar clinical efficacy but a superior safety profile for cetirizine in comparison with hydroxyzine. The main differences

Chart 63.4 Differences between first and second generation of antihistamines [6]

First-generation H1 antihistamines	Second-generation H1 antihistamines
Usually given 3–4 times a day	Usually given once or twice a day
Cross the blood–brain barrier (they are lipophilic substances, have low molecular weight and are not substrates of the P-glycoprotein efflux pump system)	Do not cross the blood–brain barrier (they are lipophobic substances, have high molecular weight, and are substrates of the P-glycoprotein efflux pump system)
Cause several adverse events (sedation, hyperactivity, insomnia, and seizures)	Do not cause significant adverse events in the absence of drug interactions
Case reports on toxicity are regularly published	Reports on serious toxicity events are virtually nonexistent
Absence of placebo-controlled, randomized, double-blind clinical trials	Some placebo controlled, randomized, double-blind clinical trials, even in children
Lethal dose already identified in infants and children	No report of fatality due to overdose

Adapted from De Benedictis et al. [110]

between first- and second-generation anti-H1 antihistamines are listed in Chart 63.4 [60, 61].

Second-generation H1-antihistamines are the only drugs for the treatment of CU supported by high levels of scientific evidence, from the perspective of evidence-based medicine, as there are prospective, randomized, and double-blind controlled studies published [2, 60]. Therefore, these medications are indicated as first-line treatment for symptomatic CU [2]. Second-generation antihistamines provide moderate to good control for 44–91% of all types of urticaria and 55% of patients with CU [62]. In general, all H1-antihistamines are effective in reducing pruritus in urticaria, although less often affecting the number and size of wheals [63]. Therefore, there is a sizable group of patients with CU for whom H1-antihistamines in doses usually recommended on-label are not able to control disease symptoms.

Some authors propose that in young adults without associated disease, the doses of

second-generation anti-H1 should be increased up to four times those recommended by manufacturers on the label, before substituting the drug or adding another medication in the treatment of CU (not approved by the National Health Surveillance Agency (ANVISA) in Brazil) [2, 56, 57, 64].

A study using cetirizine in 22 patients with CU confronted these recommendations, given that no improvement was observed after 2 weeks of treatment with 30 mg of cetirizine, although this may have been due to the limited observation period during the study [62].

Weller et al. [65] conducted a retrospective questionnaire survey on 319 patients diagnosed with spontaneous CU. The aim of this study was to establish the patients' perception on the effectiveness and adverse events of treatment with H1-antihistamines, both at standard and higher doses. Of the total population, 121 patients received questionnaires from their doctors or hospitals and 198 were informed about the research over the Internet, at the *Allergie-Centrum-Charité* homepage or at the *Urticaria Network* (www.urtikaria.net) web page. The latter group completed the questionnaire online [65]. Both questionnaires were identical. All surveys were completed anonymously and no Internet Protocol was retrieved. The only prerequisite for participation was that subjects had spontaneous CU (spontaneous wheals recurring for more than 6 weeks) and that they were adults, over 18 years of age. Participants agreed that the usual doses of second-generation antihistamines (recommended by the manufacturer) were significantly more effective than those of the first-generation drugs ($p < 0.005$) [65]. Furthermore, they found that second-generation drugs caused significantly fewer side effects ($p < 0.001$) and less sedation than first-generation antihistamine medications ($p < 0.001$) [65]. Three-quarters of the patients reported that they had increased the doses of second-generation antihistamines, and 40%, 42%, and 54% of the subjects reported significantly higher benefits by taking two, three, or four tablets per day, respectively [65]. The number of reports on adverse events and sedation with higher doses was not significantly different from those reported with usual doses [65].

In a literature review study, Sánchez-Borges et al. [66] concluded that the use of higher doses of second-generation anti-H1 increased the proportion of patients who achieved the control of urticaria symptoms, without producing higher rates of adverse events, including somnolence [66].

Despite the small number of studies, the best results seem to be those obtained with cetirizine, levocetirizine, and desloratadine; regarding dosage increase, there were mixed results with rupatadine and one study with fexofenadine failed to show greater improvement with higher doses [66].

Overall, studies comparing various second-generation anti-H1 drugs in the treatment of CU observed no significant difference regarding symptom control, quality of life, and safety profile, and all of them are designated as first-line agents in the treatment of CU [2, 61]. Chart 63.5 summarizes the recommendations for the treatment of urticaria, according to the Fourth Consensus Meeting, Urticaria 2012 held in Berlin.

An ample variety of H1-antihistamines available on the market, their dosage, and recommended doses can be seen in Chart 63.6. A recent review performed by Fedorowicz et al. [67] for the Cochrane Skin Group Specialized Register concluded that the presence of few studies and small case series in the literature regarding the use of anti-H2 (cimetidine and ranitidine) in the

Chart 63.5 Summary of the European Consensus of Chronic Urticaria (4th Consensus Meeting, Urticaria 2012) [6]

Terminology and classification	Chronic urticaria may occur as "chronic spontaneous urticaria" or "inducible chronic urticaria." The inducible group includes physical, cholinergic, contact, and aquagenic urticarias; the term "idiopathic" chronic urticaria should be avoided
Differential diagnoses	Differential diagnoses should include bradykinin-related angioedema (hereditary angioedema and angioedema secondary to angiotensin conversion inhibitors) and urticarial syndromes associated with interleukin-1 (autoinflammatory syndromes or diseases, urticaria vasculitis)

(continued)

Chart 63.5 (continued)

Determination of disease activity	(a) New methods and tools area available
	(b) Disease activity: UAS (urticaria activity score), AAS (angioedema activity score), triggering threshold of inducible urticaria
	(c) Quality of life: CU-Q2oL (chronic urticaria quality of life survey chronic urticaria), AE-QoL (angioedema quality of life survey – quality of life questionnaire for patients with angioedema)
Diagnosis	(a) In spontaneous chronic urticaria there are two steps to the diagnosis:
	Routine diagnosis (exclusion of serious underlying diseases in all patients): erythrocyte sedimentation rate or C-reactive protein, complete blood count, suspend the use of nonsteroidal anti-inflammatory drugs or substitute them
	Complementary diagnosis (to identify and treat possible causes in patients with persistent disease and/or severe spontaneous urticaria): based overall on the patient's medical history, detection of autoreactivity, intolerance, and infection
	(b) In inducible chronic urticaria, the diagnosis is limited (usually) to determining the triggering factor and the tolerance threshold to stimuli
Treatment	Treatment is indicated in three steps:
	Step 1: nonsedating, second-generation antihistamines
	Step 2: doses up to four times those recommended on the label of nonsedating, second-generation antihistamines
	Step 3: Omalizumab, cyclosporine A, montelukast

treatment of urticaria preclude any conclusion on their effectiveness in treating the disease.

Other Pharmacologic Interventions in Chronic Urticaria (Third-Line Agents)

While antihistamine treatments with high-dose second-generation anti-H1 (up to four times the recommended doses) can control the symptoms in most patients, alternative treatments may be required for the remaining unresponsive population [2]. Since the intensity of CU fluctuates, and spontaneous remission may occur in 50% of patients within 6 months of diagnosis, it is advisable to re-evaluate the need for continued treatment or alternative therapies every 3–6 months, although in our opinion patients should be assessed at interval periods no longer than 2 months [2]. There are numerous studies on alternative drugs for the treatment of CU, either in combination with H1-antihistamines or as monotherapy, albeit with low levels of scientific evidence [2]. Examples for this strategy include ketotifen, montelukast, warfarin, nifedipine, tranexamic acid, colchicine, dapsone, sulfasalazine, methotrexate, plasmapheresis, intravenous immunoglobulin, hydroxychloroquine, biological agents, danazol/stanozolol, and cyclophosphamide, among others [9]. Even with low levels of scientific evidence, many of these drugs are used in antihistamine-resistant patients with CU, and we will therefore discuss them further.

Immunosuppressors

Cyclosporine

Most studies on cyclosporine used 5 mg/kg/day doses for periods ranging from 8 to 16 weeks with good results, varying from approximately 64–95%. Some studies used smaller doses (2–5 mg/kg/day) [68–71]. At these doses, side effects occur less frequently than at higher ones. In these cases in particular there have been reports on infections, hypertension, nephrotoxicity, and increased malignancy [72, 73]. Other less severe side effects include hirsutism, headache, nausea, paresthesia, abdominal pain, and hypertension. For this reason it is necessary to monitor blood pressure, renal function, and cyclosporine levels, and even glycemia and lipidemia [72, 75].

Methotrexate

This drug has anti-inflammatory and immunosuppressive activities, although much of its mechanisms of action are unknown. It is known

Chart 63.6 Antihistamine drugs in the Brazilian market, doses for children and adults, time of action, metabolizing, drug interactions, and dose adjustment if necessary [6]

Generation	Drugs	Dose for children (day)	Dose for adults (day)	T_{max}*	Time to action (h)**	Hepatic metabolism	Drug interactions	Dose adjustment
1st	Chlorpheniramine (Dex◆)	0.15 mg/kg/day	2–8 mg/day÷3 doses	2.8 ± 0.8	3	Yes	Likely	ND
	Clemastine◆	0.5 ml/kg/day	2 mg	ND	2	Yes	Likely	ND
	Cyproheptadine◆	0.125 mg/kg/day	2–8 mg	ND	ND	Yes	Likely	LF
	Diphendhydramine	5 mg/kg ÷ 3–4 times/day	50–400 mg	1.7 ± 1.0	2	Yes	Likely	LF
	Doxepin◆	Not used	10–100 mg	2	ND	Yes	Likely	LF
	Hydroxyzine◆	1–2 mg/kg/day	10–200 mg	2.1 ± 0.4	2	Yes	Likely	LF
2nd	Acrivastine	Unavailable	Unavailable	1.4 ± 0.4	1	<50%	Unlikely	ND
	Bilastine◆	Unavailable (only >12 years old)	20 mg	1.0–1.5	1	No		
	Ketotifen◆	0.05 mg/kg/day	1–2 mg	3.6 ± 1.6	ND	Yes (?)	ND	LF and KF
	Cetiriazine◆	2–6 years, 2.5 mg; 6–12 years, 5 mg; 2×/day	10 mg	1.0 ± 0.5	1	<40%	Unlikely	IH and IR
	Loratadine◆/Descarboethoxyloratadine	2–6 years, 2.5 mg. 6–12 years, 5 mg; 1×/day	10 mg	1.2 ± 0.3 / 1.5 ± 0.7	2	Yes	Very unlikely	LF and KF
	Ebastine◆/Carebastine	2–6 years, 2.5 mg. 6–12 years, 5 mg;1×/day	60/180 mg	2.6 ± 5.7	2	Yes	Likely	LF and KF
	Fexofenadine◆	>12 years, 60 mg 2x/day	(6 months to 2 years: 2.5 ml q. 12 h) (2–11 years: 5 mg q 12 h)	26	2	<8% Yes	Yes (P-glycoprotein)	KF
	Mizolastine	Unavailable	Unavailable	1.5	1	Yes	Likely	ND
	Levocetirizine◆	<2–6 years: 5 drops q 12 h or (0.25 mg/kg/day); >6 years: 5 mg	5 mg	0.8 ± 0.5	1	<15%	Unlikely	LF and KF
	Desloratadine◆	6 months–1 year: 1 mg; 1–6 years: 1.25 mg; 6–12 years: 2.5 mg; 1×/day	5 mg	1–3	2	Yes	Unlikely	LF and KF
	Rupatadine◆	Unavailable	10 mg	0.75	2	Yes	Unlikely	

LF liver failure, *KF* kidney failure, *ND* not defined

that methotrexate increases adenosine levels, inducing the apoptosis of CD4 lymphocytes and inhibiting neutrophil chemotaxis [74, 75]. It has been used in doses of 10–15 mg per week in cases that were resistant to antihistamines and systemic corticosteroids, with results achieved after 3–6 weeks of treatment [74, 75]. It is considered a corticosteroid-sparing alternative. Gastrointestinal side effects, stomatitis, headache, fatigue, and hematologic alterations may occur at low doses [74, 75]. Since there is a risk of hepatotoxicity and myelosuppression, laboratory surveillance is mandatory, especially of hepatic function [74, 75].

Cyclophosphamide

Prescribed usually in cases of extreme treatment resistance, cyclophosphamide it has been used orally at 100-mg doses (equivalent to 1.5 mg/kg for 5 days, every week) associated with 600 mg/day acetylcysteine to reduce bladder toxicity, with good results [76]. It should be used sparingly because of its many potential adverse events [76].

Biologic Agents

Omalizumab

This is an anti-IgE monoclonal antibody approved for the treatment of moderate to severe asthma. Omalizumab decreases free IgE and inhibits the expression of high-affinity IgE receptors on mast cells and basophils [6]. Applied subcutaneously, it was one of the first biopharmaceuticals on the market indicated to treat severe allergic asthma. When treating CU, one must take into consideration the presence of IgE autoantibodies [80, 81]. Good results have been reported in idiopathic and cholinergic CU, urticaria secondary to sun or cold exposure, dermographism, and angioedema [80, 81].

A randomized multicenter, double-blinded study evaluated 90 patients aged 12–75 years with chronic spontaneous urticaria unresponsive to antihistamines, for whom good control of the disease was achieved with one dose of omalizumab [82]. The improvement obtained with the medication versus placebo was statistically significant at 300- and 600-mg doses, but not at 75 mg; complete

resolution of urticaria was achieved in the first 2 weeks in 36% of patients in the 300-mg group, 28.6% in the 600-mg group, 4.4% in the 75-mg group, and 0% in the placebo group [82]. Recently, a randomized multicenter study with 323 patients treated every 4 weeks observed, at week 16, a 44% improvement in the 300-mg group, 22% in the 150-mg group, 16% in the 75-mg group, and 5% in the placebo group [83].

Therefore, the use of omalizumab at 300- or 600-mg doses seems to be a rapid and effective treatment for patients with CU who are persistently symptomatic despite the use of anti-H1 medications [83, 84].

Recently, omalizumab treatment for urticaria has been approved in Brazil at a dose of 300 mg per month.

Intravenous Immunoglobulin

Intravenous immunoglobulin has immunomodulatory activities, including complement and cell adhesion modulation, and acts at the level of cytokines and autoantibodies. This drug has been used with good results in CU, at a dose of 0.4 mg/kg/day for 5 consecutive days, or in other schemes, also used subcutaneously [77–80]. Anaphylactoid reactions, aseptic meningitis, and renal failure are reported as rare adverse events and, despite being relatively safe, this is a very high-cost treatment.

Anti-CD20 Drugs (Rituximab and Others)

A chimeric monoclonal antibody against CD20 protein, anti-CD20 is expressed mainly on B cells (lymphocytes) [84]. Rituximab destroys B lymphocytes and decreases the production of autoantibodies. In three case reports, the drug was effective in two patients with H1-antihistamine-resistant CU and in another case it was ineffective [85–87].

Anti-Tumor Necrosis Factor α (TNF-α) Agents

Wilson et al. [88] treated six patients with CU who had unsuccessfully received a combination of H1-antihistamines and immunosuppressants, with different anti-TNF agents (four with etanercept,

one infliximab, and one adalimumab) based on previous studies that had shown elevated serum and cutaneous TNF-α in patients with CU compared with controls [89, 90]. The authors reported improvement on the urticaria, with length of remission varying from months to years, and three patients continuing in long-lasting remission even after all medications were withdrawn [88].

Corticosteroids

Corticosteroids are known to be effective in the treatment of CU in patients who are unresponsive to anti-H1 medications [84]. Nonetheless, controlled studies on the subject are still lacking. Clinical effects may be evident at 25-mg doses in the early days of treatment; however, given the potential adverse events associated with the chronic use of corticosteroids (diabetes mellitus, hypertension, osteoporosis, and gastrointestinal bleeding), oral corticosteroids should be used for short periods of time (3–7 days per month) and at the smallest effective dose [2, 84].

Drugs with Anti-inflammatory Effects

These medications are generally safe and affordable to the majority of the population and have still limited evidence of effectiveness in the literature, but can be used in the treatment of CU before more expensive or toxic drugs are considered [84].

Hydroxychloroquine
Reeves et al. [91] studied 18 patients with CU who were treated with hydroxychloroquine for 12 weeks. The treatment significantly improved the quality of life of patients, although the levels of urticaria activity were scarcely influenced. This drug is relatively safe, although it can cause retinopathy, usually after 5 years of continuous use [84].

Colchicine
There are two studies published in the indexed literature, a prospective one by Criado et al. [58] and a retrospective analysis by Pho et al. [92], evaluating the use of colchicine in the treatment of CU. The drug acts by precluding the formation of the apparatus that extrudes granules from mast cells and basophils [6]. Both studies found partial or complete response in at least half of the patients [6]. Adverse events are bearable, including diarrhea, leukopenia, and hematuria; furthermore, it is a low-cost medication [6]. Colchicine should not be used in pregnant women [6].

Dapsone
Dapsone has been reported to be effective in the treatment of CU/angioedema at doses of 25–50 mg per day [57, 58, 84, 93]. In a study in association with desloratadine and as monotherapy, it showed higher rates of remission, although urticaria activity scores were not reduced [89]. According to Noda et al. [93], dapsone's anti-inflammatory activity occurs by inhibiting the chemotactic migration of neutrophils, protecting cells from neutrophil- and eosinophil-mediated damage, reducing the release of prostaglandins and leukotrienes, and reducing the integrin-mediated neutrophil adherence, which inhibits the migration of these cells into the extravascular compartment [93].

Although generally well tolerated, dapsone can induce dose-dependent anemia and, less frequently, peripheral neuropathy, exanthema, DRESS syndrome (drug rash with eosinophilia and systemic symptoms), gastrointestinal symptoms, hepatotoxicity, and methemoglobinemia. Monitoring serum levels of glucose-6-phosphate dehydrogenase is necessary, owing to the risk of severe hemolysis in patients lacking this enzyme [84].

Sulfasalazine
The recommended dose is 2 g orally, daily, with results usually seen within a month [84]. Adverse events such as nausea, dyspepsia, headache, proteinuria, hepatotoxicity, and hematologic abnormalities have been reported [84], [94].

Leukotriene Receptor Antagonist (Montelukast)

Montelukast is used at 10 mg per day in adults, as an adjuvant drug to the antihistamine treatment,

with excellent safety profile [58, 84]. Leukotrienes C4, D4, and E4 play an important role in the process of allergic inflammation, warranting this drug as an adjunct in the treatment of CU. Khan and Lynch [95] achieved CU control in 48% of 25 patients treated with montelukast associated with anti-H1 and anti-H2, whereby 11 had no improvement and in two patients the urticaria worsened after the drug was introduced. Adverse events included upper respiratory tract symptoms, diarrhea, nausea, vomiting, exanthema, elevated transaminases, and, exceptionally, psychiatric disorders [95].

Anticoagulants

Frequently patients with CU show an increase in plasma markers of thrombin generation and fibrinolysis during periods of disease exacerbation, perhaps as a consequence of tissue factor expression on the plasma membrane of activated eosinophils [84, 96]. The activation of coagulation and fibrinolysis decreases as the disease enters remission [84]. The exact role of this phenomenon (activation of coagulation and fibrinolysis) acting as the centerpiece of the disease's pathophysiology or epiphenomenon, acting as an amplifier of inflammation, is not yet elucidated.

According to Asero et al. [84] it seems reasonable to use anticoagulant or antifibrinolytic agents in patients with CU, since the disease's activity runs parallel to this phenomenon. Reports on the use of oral anticoagulation, warfarin (keeping international normalized ratio >2), and heparin have been published for the last decade [97–100]. However, the use of these drugs is still not routinely recommended in the treatment of CU [84].

Levothyroxine

The association between thyroid autoimmunity and CU is well established. Karaayvaz et al. [101] conducted a study with 60 patients with UC, divided into two groups matched for sex and age, using ketotifen or levocetirizine. The group using ketotifen achieved symptom relief while taking the medication, but relapsed after drug withdrawal. Eighteen patients in the group using levothyroxine achieved complete remission and three had partial improvements; furthermore, symptoms did not recur in those with complete response [101].

Treatment with levothyroxine takes at least 10 days to demonstrate an effect; 0.1 mg/kg/day for 4 weeks is usually appropriate and does not cause alterations in thyroid function [101]. It is advisable to approach these cases in conjunction with an endocrinologist, especially in situations where no control of CU associated with thyroid autoimmunity was obtained with other pharmacologic interventions and provided there are no contraindications to thyroid hormone replacement therapy [101].

It is hypothesized that patients with autoimmune thyroiditis have autoantibodies against thyroid proteins (antithyroglobulin and antiperoxidase), which induce inflammation and cytokine release that will subsequently bind to C4, activate the complement system, and stimulate the release of histamine by basophils and mast cells [102]. Thus, antithyroid and anti-FcεRIα antibodies activate the complement in a synergic manner, increasing the release of vasoactive amines and leading to urticaria [6].

Therapeutic Strategies in Clinical Practice

In our understanding, the treatment of CU should be customized according to patients' lifestyles (profession, social interactions, and recreational activities), their socioeconomic level, and understanding of disease and treatment. A basic principle is to avoid known aggravating or triggering agents, such as alcohol and indiscriminate use of cyclooxygenase inhibitors and nonsteroidal anti-inflammatory drugs. Each therapeutic intervention cannot be assessed as to its effectiveness before 2–4 weeks, at the earliest. If disease control is not achieved with a certain drug, as long as there is no contraindication for an association, it should be maintained at least until the illness is controlled.

Patients with CU tend to develop psychological/psychiatric problems, some even preceding the initial event of urticaria, such as post-traumatic stress disorder, alexithymia (marked difficulty in verbalizing emotions, describing feelings or bodily sensations), anxiety (particularly phobias) and depression, which may affect up to 48% of patients with spontaneous CU [103–105]. Thus, psychological and/or psychiatric support, beside positive attitudes from the health care team, can always be helpful to the treatment.

The quality of life of patients with CU is greatly affected, as patients suffer with pruritus and wheals, and present fatigue caused by sleep disorders and adverse events of medications [106]. The disease affects many realms of the patient's life, also having an economic impact for the patient and the health system [106]. In tertiary referral centers, the impact on quality of life for these patients is comparable with that experienced by older subjects with severe ischemic heart disease and overall, in various dimensions, with the impact suffered by patients with psoriasis and atopic dermatitis [106].

Therefore, facing up to the reality of medical practice in Brazil, we adopted a strategy of sequential treatment (in steps), ranging from the use of anti-H1 as standard initial drugs, to second-line agents (leukotrienes and corticosteroids in short courses), third-line medications (omalizumab, cyclosporine, methotrexate; anti-inflammatory drugs, such as dapsone, hydroxychloroquine, and colchicine), and fourth-line drugs (immunosuppressants that are more toxic), considering that in most cases progression to the next level of therapy also implies an increase in direct or indirect costs, as well as greater risks of adverse events (Fig. 63.6) [84].

Chronic Urticaria: Severity Markers and Disease Prognosis

Rabelo-Filardi et al. [107], in a systematic review of 34 studies published on spontaneous CU, concluded that the clinical severity of CU can forecast disease duration, and laboratory parameters such as elevation of serum levels of fragments 1+2 prothrombin, D-dimer, and C-reactive protein may reflect the gravity of the disease, and perhaps its resistance to conventional treatment. Patients with more severe symptoms may have more persistent disease courses [108]. Spontaneous remissions occur in 30–50% of patients within a year of disease evolution, and another 20% within 5 years [108]. About 20% of patients with CU remain ill after 5 years of evolution [108]. Nearly half of patients with CU lasting 6 months will probably still have the disease 10 years later [108].

A Korean study of 131 patients with CU evaluated the presence of signs of metabolic syndrome (MetS), disease activity score, and serum markers for inflammatory activity [109]. Thirty-nine patients (28.9%) had MetS compared with 17.8% of subjects in the matched control group ($p = 0.001$). Patients with CU and metabolic syndrome were older, had higher mean scores of disease activity, and higher levels of serum eosinophil cationic protein (ECP), TNF-α, and complement system factors, besides higher frequency of negative tetrachlorosalicylanilide when compared with patients with CU without MetS. Logistic regression showed that an urticaria activity score ≥13 ($p = 0.025$) and the presence of MetS ($p = 0.036$) were independent predictors of a likely difficult-to-treat CU [109]. Therefore, both CU and MetS may share low-grade chronic inflammation, involving TNF-α, ECP, and C3, which may be mutually triggering or exacerbating the disease [109]. Future studies will better elucidate subsequent disorders in patients with CU, since the disease may course with coexisting MetS, activation of coagulation/fibrinolysis, and chronic inflammation, which may represent potential cardiovascular diseases and diabetes mellitus during the life of these patients.

Summary
- CU is currently classified as spontaneous or induced by physical stimuli. Convention determined that the term "idiopathic" should be avoided

- Studies with larger samples should be conducted in the future to assess the value of screening and treatment of infectious and parasitic agents in the course of CU, especially in endemic areas
- The presence of autoreactivity in patients with spontaneous CU can be demonstrated in 50% of cases, in a simple manner, by the autologous serum skin test;
- The vast majority of CUs are not IgE-mediated allergic diseases
- The diagnosis of autoimmune CU should be based on strict criteria established by the European consensus
- The link between inflammation and coagulation, boosting the mediator release cascade, was demonstrated in a group of patients with CU and high levels of eosinophilic activation
- First-line treatment of CU in the first decade of this century is based on second-generation antihistamines; however, in some patients it is necessary to combine these with anti-inflammatory or immunosuppressive drugs, besides the promising use of immunobiological agents such as omalizumab

Similar to some cases of psoriasis, spontaneous CU can have a major impact on patients' quality of life, and also in the various realms of the psyche. Further studies will confirm or deny the progressive course of metabolic syndrome and cardiovascular complications among patients with long lasting spontaneous CU.

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Erythema Nodosum

64

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Key Points

- Erythema nodosum (EN) is the most frequent form of panniculitis
- EN is mainly idiopathic, but can be a reaction pattern from a wide variety of etiologic agents
- The lesions are subcutaneous nodules clinically manifested as erythematous and painful patches located symmetrically on the anterior surface of the lower extremities
- Histologically EN is characterized by a predominantly septal panniculitis without vasculitis
- EN prevails in women between 15 and 30 years of age
- Early diagnosis in primary care is necessary to guide investigation and treat the underlying cause

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Introduction

Panniculitis is inflammation of the subcutaneous adipose tissue and is an uncommon pathology characterized by sudden inflammatory patches or nodules under the skin. Erythema nodosum (EN) is the most common clinical presentation of panniculitis, affecting 1–5 per 100,000 persons per year. The highest incidence is in young women from 15 to 30 years of age, and the male-to-female ratio is 1:6 [12]. In children the ratio between the genders is 1:1 [10, 11].

EN is nowadays considered a reaction pattern resulting from a wide variety of etiologic agents [1, 2]. About 55% of EN are classified as idiopathic [1, 18]. Infections are the most common etiology of EN in children, mainly streptococcal pharyngitis, and the main causes in the adult population are medicaments, systemic inflammatory diseases (sarcoidosis, inflammatory bowel disease), pregnancy, and malignancy.

The classic clinical presentation of EN is painful and symmetric nodules of imprecise limits on the tibial anterior surface. Characteristically the nodules are more palpable than visible. Frequently it consists of a

potentially grave systemic disease manifestation, and for this reason it must be promptly recognized so that the etiologic investigation and correct treatment can be instigated as early as possible.

Concepts

Currently there is a tendency to classify EN not as a disease itself but as a nonspecific pattern of reaction from different types of antigens. Many different immunologic patterns are involved in its immunopathology, the most important of them being delayed type 4 hypersensitivity.

Despite exhaustive investigation more than 50% of cases remain without related etiology, being classified as idiopathic. The main causes of EN are listed in Table 64.1.

The main recognizable cause of EN is streptococcal pharyngitis (caused by group A β-hemolytic streptococci), which is more likely to occur in the young. The skin lesions appear from 2 to 4 weeks after the pharyngeal infection and are accompanied by high levels of antistreptolysin O (ASLO) and/or anti-DNase B. Other possible streptococcal infections should be searched for, such as impetigo, cellulitis, intertrigo (axilla, perineum), vulvovaginitis, balanitis, and infection of the perianal area. Group A β-hemolytic *Streptococcus* can also be found by rapid diagnostic testing or collection of a secretion culture from the suspected areas.

EN can often be the first sign of a systemic disease such as tuberculosis, profound fungal infection, sarcoidosis, inflammatory bowel disease, and malignancy [13].

Many single case reports document other possible associations, including reports of EN in the setting of vaccinations [1, 8, 23, 24].

Table 64.1 Causes of EN

Common	Rare (<1%)
Idiopathic (up to 55%)	Vaccine
	Tuberculosis, cholera, hepatitis B, human papillomavirus, malaria, rabies, smallpox, typhoid, tetanus–diphtheria–acellular pertussis (Tdap)
Infections	Infections
Bacterial:	Bacterial:
Streptococcal pharyngitis (28–48%), tuberculosis, yersiniosis, *Mycoplasma*, *Chlamydia*	*Salmonella*, *Campylobacter*, *Shigella*, brucellosis, psittacosis, *Rickettsia*, syphilis
Fungal:	Fungal:
Histoplasmosis, coccidioidomycosis	Blastomycosis, sporotrichosis, dermatophytosis
	Viral:
	Infectious mononucleosis, hepatitis B, hepatitis C, herpes simplex virus, human immunodeficiency virus
	Parasitosis:
	Amoebiasis, giardiasis, ascariasis
Systemic disease:	Systemic disease:
Sarcoidosis (11–25%)	Behcet's disease
With bilateral hilar adenopathy	
Enteropathies (1–4%):	
Ulcerative colitis and Crohn's disease	
Drugs (3–10%):	Drugs:
Antibiotics (e.g., sulfonamides, penicillin), oral contraceptives, bromides, iodide	Minocycline, gold salts, salicylates
Pregnancy (2–5%)	Malignancies:
	Hodgkin's lymphoma, non-Hodgkin lymphoma, leukemia, renal cell carcinoma
	Miscellany:
	Vitamin B12 deficiency

Clinical Presentation

EN is characterized by painful, erythematous, and symmetric subcutaneous nodules of imprecise limits. The size of the lesions varies from 0.5 to 10 cm in diameter [2]. The most frequent location is the tibial anterior surface, but the extensor surface of forearms, thighs, chest, and even the face can also be involved (Fig. 64.1).

The nodules are of sudden appearance. Individually they tend to decline in 2 weeks, although new outcroppings persist for up to 6 weeks. Complete healing often takes 1–2 months when the nodules assume a bruise-like appearance, also known as "erythema contusiformis." They can leave local hyperchromia but no atrophy or scars because there is no ulcer formation.

EN usually occurs at the end of the winter and the beginning of spring. Prodromal symptoms such as low-grade fever (60%), malaise (67%), arthralgias (64%), arthritis (31%) [1], cough, and weight loss may often precede the onset of the lesions by 1–3 weeks. Arthralgias can also persist for up to 2 years after the resolution of the cutaneous lesions, causing nonspecific destructive joint changes [2].

Rare clinical variants of the disease are recognized [2]. EN migrans consists of persistent but minimally symptomatic unilateral nodules that tend to migrate centrifugally. Subacute nodular migratory panniculitis can reach 20 cm in diameter by confluence of the nodules on the legs. Another rare form of EN is seen in children after physical activity and affects unilaterally the palmoplantar surface.

The earlier the diagnosis is made, the earlier the underlying disease can be investigated and found.

Some clinical symptoms and physical findings should draw attention to causes associated with EN. The main symptoms are listed in Box 64.1.

Box 64.1 Findings Suggestive of Erythema Nodosum with Systemic Cause

Arthritis/synovitis

Diarrhea

History of previous upper respiratory infection

Rising ASLO titers, positive throat swab culture, or rapid test for group A *Streptococcus*

Abnormal chest X-ray

Positive skin tuberculin test

Diagnosis

The syndromic diagnosis is clinical, taking into account the sudden onset of the pretibial painful nodular lesions, generally associated with constitutional symptoms (Box 64.2).

Box 64.2 Clinical Criteria for Diagnosis of Erythema Nodosum

1. Painful erythematous or purple nodules or patches, with irregular and poorly defined borders, from 1 to 5 cm

2. Symmetric tibial anterior surface lesions, reaching or not reaching other skin areas

3. Lesions of sudden appearance, each one lasting less than 8 weeks

4. Resolution without ulceration or scars

Fig. 64.1 Erythema nodosum: erythematous nodules (Courtesy of Dermatology Service of UFCSPA)

Histopathologic examination can help in doubtful cases and rule out other diseases such as other kinds of panniculitis, but it is not pathognomonic. The microscopic aspects vary considerably according to the evolutionary stage of the lesions, although the local and type of inflammation can vary between different samples of the same panniculitis regardless of the time of evolution of the disease. Therefore, currently there is a tendency to classify panniculitis as predominantly septal panniculitis and predominantly lobular panniculitis. Other anatomopathologic data that help to guide the diagnosis are the presence or absence of fat necrosis, type of necrosis, presence or absence of vascular alteration (vasculitis, thrombosis) and presence or absence of other findings such as sclerosis and infectious agents [12].

The specimen for histopathology must be obtained through profound incisional or excisional biopsy, since punch biopsy produces inadequate samples for subcutaneous tissue visualization [10]. The histopathologic findings of EN include inflammation of the subcutaneous septum (septal panniculitis, Fig. 64.2), and perivascular inflammatory infiltrate with neutrophil predominance, edema, and hemorrhage-determined septum thickening in early lesions. In later stages granulomatous lesions can be seen in the septum (typically radial or Miescher granulomas) [10].

The etiologic investigation must be guided by the clinical symptoms and must include biochemical analysis, serologic testing, streptococcal infection research, culture examination, X-ray, pregnancy test, and Mantoux skin test.

In the pediatric demographic the most prevailing is the infectious diagnosis for EN (up to 68%), in the main being associated with streptococcal pharyngitis. However, as some studies show significant involvement of gastrointestinal infections, a stool test is imperative for children [1, 20].

Increase of nonspecific inflammatory tests such as erythrocyte sedimentation rate and C-reactive protein are regularly seen, associated or not with leukocytosis.

Differential Diagnoses

The main differential diagnoses of EN are listed in Table 64.2. One major differential that must be highlighted is the type II leprosy reactional episode, also called leprosy EN. This reactional episode can be the first manifestation of the disease and usually happens during and after leprosy treatment, with sudden appearances of painful nodular lesions not only in the anterior tibial region but primarily in the arms, abdomen, and lower limbs. Another different feature is that
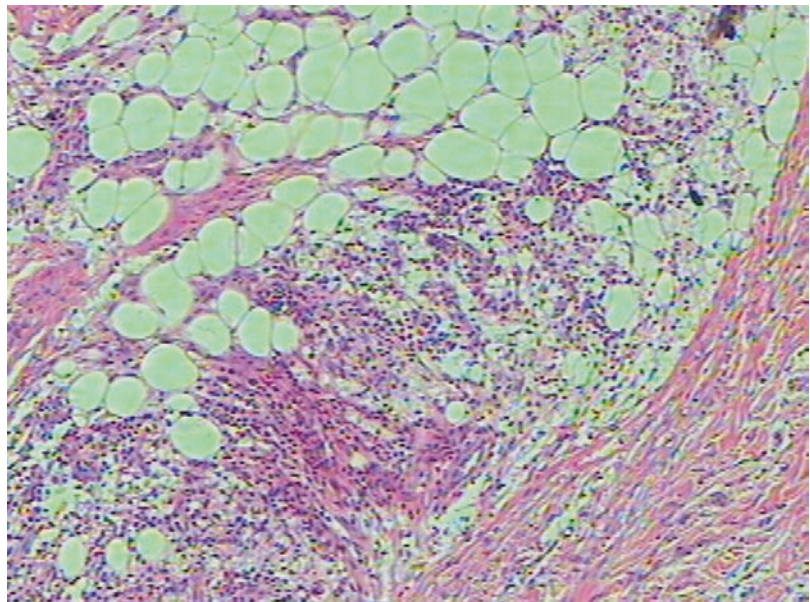
Fig. 64.2 Histopathology of erythema nodosum: septal panniculitis (Courtesy of Dermatology Service of UFCSPA)

Table 64.2 Differential diagnosis of erythema nodosum

Other panniculitis		Other diseases (occasional differential diagnostic)
Panniculitis predominantly lobular:	Other panniculitis predominantly septal	Pretibial myxedema
More common	Polyarteritis nodosa	Necrobiosis lipoidica
α1-Antitrypsin deficiency	Eosinophilic fasciitis	Necrobiotic xanthogranuloma
Cytophagic histiocytic panniculitis (a lymphoma)	Eosinophilia-myalgia syndrome	Gum (tertiary syphilis)
Lupus erythematosus profundus (lupus panniculitis)	Scleroderma	
Nodular fat necrosis	Thrombophlebitis	
Rare		
Cold panniculitis		
Infectious panniculitis		
Leukemic fat infiltrates		
Poststeroid panniculitis		
Povidone panniculitis		
Scleroderma neonatorum		
Sclerosing panniculitis		
Pancreatic panniculitis		
Lipodystrophies		
Subcutaneous fat necrosis of the newborn		
Idiopathic lobular panniculitis (Pfeiffer-Weber-Christian disease)		
Nodular vasculitis (erythema induratum)		

leprosy nodules can evolve with ulceration. It is considered an immune reaction to a multibacillary disease and usually is associated with systemic symptoms such as fever, malaise, and fatigue. It can also affect other organs such as joints, eyes, and testicles [33]. Treatment consists of prednisone and thalidomide (for men and women after childbearing age).

Therapeutic Approach

Since EN is a self-limited condition, whenever possible the treatment should be directed to its etiologic cause.

Symptomatic treatment is based on rest and elevation of the affected extremities. Nonsteroidal anti-inflammatory drugs (NSAIDs) are helpful in relieving the pain, with satisfactory outcome in most of the cases; however, they must be avoided in those cases of EN that are due to Crohn's disease because of the risk of flare and bleeding [6].

More aggressive treatments are restricted to recurrent or difficult cases.

Corticosteroids have a prompt response, but should be initiated only if infection and malignancy are discarded as possible causes of EN (due to the possibility of sepsis and spread). Commonly prednisone is used at a daily oral dose of 60 mg or 1 mg per kg body weight [1, 2].

It is important to bear in mind that prednisone can lead to a false-negative Mantoux skin test and delay the diagnosis of tuberculosis. It should therefore be avoided during early onset of the symptoms, especially in endemic areas.

Potassium iodide can be a therapeutic alternative at a dose of 400–900 mg per day, being more effective the earlier it is started. Attention should be paid to the risk of secondary hyperthyroidism development with prolonged use of this medication [4].

Other treatments can be proposed according to the underlying pathology, such as colchicine for EN associated with Behcet's disease [5, 15] and hydroxychloroquine, thalidomide, cyclosporine, and infliximab in monotherapy or combined with corticosteroids in those cases linked to Crohn's disease [7].

Even in patients with idiopathic EN, the use of tumor necrosis factor α (TNF) inhibitors can be considered in refractory cases. Some case reports indicate a satisfactory and sustained outcome with the use of subcutaneous etanercept at the dose of 25 mg twice a week in patients who had treatment failure with prednisone, potassium iodide, dapsone, NSAIDs, and methotrexate [15, 17, 25].

Other therapeutic options are mycophenolate mofetil and dapsone, depending on the clinical context. Table 64.3 shows the level of evidence regarding management.

Table 64.3 Treatment recommendations for erythema nodosum

Key for clinical practice	Level of evidence	References
Once diagnosed, etiologic search must be made according to clinical symptoms and age group of the patient	C	[1, 12]
In children, up to 68% of the cases are secondary to infectious processes, mainly streptococcal pharyngitis and bacterial gastroenteritis	C	[9, 20]
Histopathologic exam reveals septal panniculitis without vasculitis, but it is not pathognomonic	C	[10, 12, 13]
Painful symptoms are solved in the most cases by rest, elevation of the affected limbs, and use of NSAIDs	C	[1, 2]
Prednisone can be started only after infection and malignancy are discarded as possible causes	C	[1, 2]
Patients who react strongly to a Mantoux skin test must receive treatment for tuberculosis even without evidence of active infectious focus, especially in endemic areas	C	[15, 15]
Anti-TNF drugs are a promising treatment to refractory idiopathic erythema nodosum	C	[17]

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. Levels according to Strength of Recommendation Taxonomy (SORT)

Etiologic Treatment: The Impact of Etiologies Associated with EN

Streptococcal Pharyngitis

Streptococcal pharyngitis is the most identifiable disease related to EN. EN begins about 2–3 weeks after the onset of acute pharyngitis.

Epidemiologically about 15–30% cases of acute pharyngitis in children and teenagers and about 5–10% in adults are caused by group A β-hemolytic streptococci [31, 32]. The etiologic investigation can be made by culture of the throat swab, streptococcal ASLO titers, and rapid antigen detection testing (RADT). In children and teenagers, if RADT is negative, because of its lower sensitivity it is recommended that the diagnosis be confirmed with culture of the oropharynx swab (golden pattern). On the other hand, because of the low incidence of streptococcal pharyngitis in adults, the negative result of RADT in this population is an isolated acceptable alternative [32]. In the case of a positive RADT result, treatment must be initiated because of the high specificity (>95%) of the test.

The treatment of choice for this condition is antibiotics of the penicillin group, because of the high effectiveness, low cost, and safety of these drugs. For patients allergic to penicillin, erythromycin is a suitable choice. First-generation cephalosporins can be used as well, since the patient does not manifest immediate-type hypersensitivity to β-lactam antibiotics. Sulfonamides and tetracycline should be avoided because of evidence of increased rates of bacterial resistance.

Tuberculosis and Atypical Mycobacteriosis

The association between EN and tuberculosis is well established. EN can appear together with primary tuberculosis, in reactivation episodes, associated with latent tuberculosis, BCG vaccination, and after PPD (Mantoux) test [14, 15, 22].

In every case of EN a risk stratification must be made for tuberculosis with X-ray, tuberculin

skin test, and direct search for acid-/alcohol-resistant bacilli. The culture examination can also help to diagnose tuberculosis and suspected cases of atypical mycobacteriosis [10, 14].

Some atypical mycobacteria have been associated with EN, such as *Mycobacterium marinum* (common in swimming pools). In this subgroup it is important that the species is identified to provide specific treatment for the causal agent [10, 19].

In a retrospective analysis by Kumar et al. of a total of 52 patients diagnosed with idiopathic EN with a strongly positive Mantoux test (average of 19 mm), after treatment with antitubercular drugs new lesions stopped appearing in 45 patients within 6–8 weeks and subsided in 2 (data could be analyzed in 47 patients). The therapy was well tolerated except for jaundice in one patient and transient urticarial lesions in another.

Because of the strong association between EN and tuberculosis, a positive Mantoux test is an indication to receive antitubercular therapy, even without evidence of identifiable infectious focus, mainly in endemic areas [14].

Sarcoidosis

Sarcoidosis is a systemic inflammatory disease of unknown cause, characterized by noncaseating granulomas that can attack a number of organs.

The systemic clinical manifestations are various, most frequently reaching the respiratory tract, but also often affecting ocular, skin, and musculoskeletal systems.

Skin manifestations of sarcoidosis are divided into specific and nonspecific according to the presence of the noncaseating granulomas. Among the nonspecific manifestations the most common is EN, affecting 10% of patients [27].

EN in sarcoidosis prevails in young women and generally has a benign course.

When EN presents in association with pulmonary manifestations (bilateral hilar lymphadenopathy) and polyarthritis, it is known as Löfgren's syndrome. The Löfgren syndrome tends to be acute and self-limited, and usually resolves within 6–8 weeks.

Acute lesions usually require only symptomatic treatment. When cutaneous lesion is the predominant impairment of sarcoidosis the drug of choice is prednisone, and the dosage regimen should be adjusted according to the progression and severity of the disease [27].

Pregnancy and Oral Contraceptives

The immune mechanism of pregnancy and oral contraceptive use in the induction of EN is not fully elucidated. Immune complexes may play a role in the pathogenesis of EN during pregnancy, or EN may be a hypersensitivity reaction to either estrogens or progesterone [6].

As it is often a self-limited condition and various medications available to treat EN are contraindicated in pregnancy, initial treatment can involve rest, elevation of the limbs, and compression stockings, which often lead to resolution. In more resistant cases the choice of treatment should be made preferably together with obstetrics, with risk/benefit of the treatment being taken into account [3, 6].

When EN is associated with the use of oral contraceptives, the suspension of medication and symptomatic treatment of the skin lesions is recommended.

Inflammatory Bowel Disease (IBD)

IBD is often associated with nonintestinal manifestations. EN is the most observed cutaneous manifestation, predominating in females and varying from 4% to 10% of patients with IBD [28, 30]. In patients with Crohn's disease it is seen more in patients with ileocolonic disease than in those with small intestine disease [28, 30].

EN may precede the onset or follow the course of the disease. The appearance of EN lesions associated with diarrhea and abdominal pain can lead to disease flare. Improvement in the frequency of skin crises may indicate stability of the intestinal disease [29]. There is no association between EN and severity of IBD [28].

Behcet's Disease

Behcet's disease is a systemic vasculitis of unknown cause that affects veins and arteries from small to large caliber. The mucocutaneous manifestations are characteristic of the syndrome and include oral and genital ulcers, pustulosis, and EN [26].

The EN lesions related to Behcet's disease usually present in lower limb extremities, and can evolve with healing to residual skin pigmentation. Histologic examination of these lesions is characterized by elements of vasculitis, which is a sufficient finding to differentiate them from EN related to other etiologies [26].

Colchicine is the drug of choice when EN is the dominant manifestation in Behcet's disease [5, 15]. Manifestations resistant to colchicine may be treated with azathioprine and thalidomide; in more severe cases immunobiological therapy with TNF antagonists are considered [16, 17].

Medications

About 1–3% of EN is credited to medications. The main associated drugs are sulfonamides, penicillin, oral contraceptives, bromides, and iodide.

In cases of EN in patients receiving medications known to be associated with it, the drug should be discontinued whenever possible.

Malignancies

Rarely, neoplastic diseases are implicated as being responsible for triggering EN. In the absence of associated clinical symptoms, more complete diagnostic investigation for malignancies is only justified in cases of refractory EN.

The most frequently associated cancers are leukemia and lymphoma. Neoplasms of solid organs such as carcinoid tumor, colorectal, renal, and pancreatic cancer are eventually seen in association with EN.

Future Perspectives

Multiple causes of EN are currently known. However, as observational studies are conducted, idiopathic EN rates continue to remain high. In line with technological improvements in diagnostic methods, new etiologic agents are emerging as possible causes of EN.

In a case report of chronic EN, lesions without response to NSAIDs in a patient with restricted diet and vitamin B12 deficiency achieved resolution with vitamin replacement. Thus, vitamin B12 deficiency is presented as a new possible cause of EN and should be borne in mind especially in populations at higher risk of vitamin deficiency [21].

For refractory cases, immunobiological therapy with the use of TNF antagonists is emerging as a potential treatment. Case reports indicate an excellent response in more severe and refractory cases to already established drugs [17, 25].

Glossary

Gumma Solid formation characterized by nodules that liquefies in its central portion, and may ulcerate. Typical lesion of tertiary syphilis. Common in skin, but may occur in other organs such as liver, bone, and testis.

Panniculitis Inflammation of the adipose tissue. Also called hypodermitis.

Punch biopsy Skin biopsy performed with cylindrical instruments that can range from 2 to 8 mm.

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Leg Ulcers and Lymphedema

65

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Chronic Leg Ulcers

Introduction

Chronic leg ulcer is defined as an ulcer in the skin below the level of the knee persisting for more than 6 weeks and showing no tendency to heal after 3 or more months. It is a relatively common condition among adults, with multiple causes (Charts 65.1 and 65.2), the main ones being venous disease, arterial disease, and neuropathy [1].

These ulcers affect large portion of the adult population and cause a significant social and economic impact in terms of medical and nursing care, absence from work, and adverse impact on patients' quality of life.

Venous Ulcer

Epidemiology

Venous ulcer (VU), the most advanced stage of chronic venous disease, is a common problem in Western countries and represents the most com-

mon entity, accounting for 51–70% of all chronic leg ulcers [2]. The prevalence of VU varies between 0.06% and 2%, occurring in approximately 4% of adults over 65 years [3].

Complications arising from VU are diverse, primarily related to its chronicity and high rates of relapse after healing. In addition, the physical, social, economic, and emotional burdens are sizable [4, 5]. The overall costs of treatment of patients with VUs in most Western countries constitutes approximately 1% of the entire health care budgets [6].

Etiopathogenesis

VU is caused by a dysfunction in the muscular pump of the calf, which is the primary mechanism for the return of blood from the lower limbs to the heart. It comprises calf muscles, the deep venous system, the superficial venous system, and the perforating/communicating vein system. Pump dysfunction can result from deep venous insufficiency (primary or post-thrombotic), deep venous obstruction, perforating insufficiency, superficial venous insufficiency, arteriovenous fistulas, neuromuscular dysfunction, or a combination of these factors. However, the two main causes of dysfunction in the calf muscle pump are primary varicose diseases and late effects of deep venous thrombosis (post-thrombotic or postphlebitic syndrome) [7].

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Chart 65.1 Main aspects of the three main causes of chronic leg ulcers

Chronic leg ulcers	Features
Venous ulcer	The most common entity accounting for 51–70% of all chronic leg ulcers It occurs in the distal portion of the legs The surrounding skin is erythematous or hyperpigmented with variable degrees of induration Varicose veins and ankle edema are common The pulses of the lower limbs are usually normal, and ABI greater than 0.9 Compression therapy: the main methods for healing
Arterial ulcer	10–25% of cases of chronic leg ulcers Ulcers occur mainly on bony prominences of the feet, ankles, and heels The main symptom associated is intermittent claudication and pain during resting The affected limb is often colder, with pallor during lifting and flushing when pending; absence of peripheral pulses ABI (ankle-brachial index) below 0.9 Assessment of the vascular surgeon; limbs with critical ischemia may benefit from bypass surgery or angioplasty Drug treatments: aspirin, clopidogrel, and cilostazol
Neuropathic ulcers	Main causes are *diabetes mellitus* and leprosy It occurs particularly in trauma sites; the perforating plantar ulcer is the typical representative and it is painless ulcer, deep with calloused edges The test of Semmes-Weinstein: If the patient is unable to detect the test when using monofilaments in the plantar region, this is considered with loss of protective sensation Management: preventive, local treatment of ulcer, and measures to reduce plantar pressure

Chart 65.2 Main aspects of the less common causes of chronic leg ulcers

Chronic leg ulcers less common	Features
Hypertensive ischemic ulcer (Martorell ulcer)	Patients with uncontrolled arterial hypertension The ulcers often are extremely painful, located in the anterolateral and posterior portions of the legs, and may have purplish color or erythema in the periphery of the ulcer Peripheral pulses are palpable and ABI (ankle-brachial index) is greater than 0.9 The reduction and control of blood pressure is the best therapeutic measure It is important to replace beta-blockers for other classes of antihypertensive drugs
Pyoderma gangrenosum	It is considered an inflammatory ulcer The pathogenesis remains unknown, but it is probably related to a hyperergic reaction The disease begins as a papule, vesicle, or pustules that quickly ulcerate, generating a very painful injury. The ulcers are necrotic and have purpura and undermined borders It is frequently associated with Crohn's disease, ulcerative colitis, rheumatoid arthritis, and myeloproliferative diseases The treatment is mainly with immunosuppressors as systemic corticosteroids
Rheumatoid arthritis ulcers	Ulcers can be due to chronic venous insufficiency, vasculitis disease activity, or pyoderma gangrenosum
Vasculitis	The lesion begins with purpuric and necrotic areas that later progress to ulceration. Examples: leukocytoclastic vasculitis, cryoglobulinemia, Henoch-Schönlein purpura, polyarteritis nodosa, Churg-Strauss syndrome, and Wegener's granulomatosis The treatment follows the cause

(continued)

Chart 65.2 (continued)

Chronic leg ulcers less common	Features
Thrombophilia	The ulcers are characterized by pain, gangrene, and lower limb ischemia, preceded by livedo reticularis and white atrophy The antiphospholipid syndrome is the main condition of acquired thrombophilia
Livedoid vasculopathy	Small and recurrent ulcers characterized by painful purple macules and papules that subsequently ulcerate The ulcers heal over weeks to months resulting in smooth, porcelain-white, atrophic plaque-like areas with surrounding telangiectasia and hyperpigmentation Treatment: anticoagulants, antiplatelet agents (aspirin, dipyridamole), pentoxifylline, danazol, and other fibrinolytic agents. Additional measures such as rest and compression therapy are also important
Hematological diseases	Sickle cell anemia, thalassemia, thrombotic thrombocytosis, and polycythemia vera are responsible for chronic leg ulcers
Infections	Leishmaniasis: the ulcers are usually circular, with infiltrated borders and granular clean wound bed Paracoccidioidomycosis: the ulcers may have a wound bed with hemorrhagic dotted appearance
Neoplasia	Squamous cell carcinoma, basal cell carcinoma, and lymphomas as primary neoplastic ulcers Neoplastic transformation of chronic ulcers such as in long-term venous ulcers, which may undergo malignant transformation into squamous or basal cell carcinoma, and these are called Marjolin's ulcers
Lymphedema	Injuries and subsequent infections can lead to formation of ulcers. The treatment is based on the local care of the ulcer and compression therapy

(continued)

Chart 65.2 (continued)

Chronic leg ulcers less common	Features
Other causes	Ulcers secondary to occlusion vascular due to drugs: warfarin and hydroxyurea Necrobiosis lipoidica Ulcers as manifestations of microvascular occlusion syndromes: cryoglobulins, cryofibrinogen, vascular occlusion by cholesterol emboli and oxalate, calciphylaxis, vascular coagulopathy (Sneddon syndrome), vascular invasion by microorganisms (ecthyma gangrenosum, opportunistic fungi, Lucio's phenomenon in leprosy)

Valvular incompetence of the venous system has been implicated as a major factor in the development of VUs, which may compromise the superficial venous system, deep and perforating, alone or in combination. When venous valves are damaged, blood reflux from the deep to the superficial veins occurs and, consequently, venous hypertension develops. This continuous hypertension in veins, venules, and capillaries is responsible for typical alterations associated with VU. However, the mechanism by which this hypertension causes alterations remains unclear despite some theories that attempt to explain its pathogenesis. The most recently advanced theories associate the origin of the ulcer with microcirculatory abnormalities and the generation of an inflammatory response [8].

Other factors described include the inflammatory status, chronic nonhealing VUs, such as excess metalloproteinase (MMP), and cytokine imbalance. MMPs, a family of zinc-dependent endoproteinases, are known for their tissue-remodeling properties. In general this family of enzymes is not expressed in healthy tissue, although in the remodeling processes it does increase. Moreover, tissue inhibitors of metalloproteinases (TIMPs) have been extensively studied because of their ability to avoid excessive breakdown of extracellular matrix [9].

An orchestrated balance between MMPs and TIMPs is necessary for proper healing. Imbalance can lead to accumulation of MMPs, resulting in uncontrolled proteolysis, as seen in chronic inflammatory conditions.

Clinical Presentation

In general, the VU is an irregularly shaped wound, initially superficial, with well-defined borders. The surrounding skin is erythematous or hyperpigmented with variable degrees of induration (acute or chronic lipodermosclerosis). Yellowish exudate is usually observed. The size and site of ulcers vary, but they usually occur in the distal portion of the lower limbs. Varicose veins and ankle edema are common [10] (Fig. 65.1).

The pain is frequent and of variable intensity, generally worsening toward the day's end and in a standing position, and improves with limb elevation. When the pain is very strong, especially with limb elevation, arterial disease as a cause must be ruled out [11].

Between 58% and 86% of patients have eczema around the ulcer, as evidenced by erythema, scaling, and pruritus, and augmented by topical medications, particularly antibiotics and lanolin [12].

The main complications that occur in patients with chronic venous ulcers are infections of soft tissue, critical colonization, contact dermatitis, osteomyelitis and, less frequently, neoplastic transformation.

Complementary Test

The diagnosis of VU is based primarily on clinical criteria. Complementary laboratory tests such as duplex scanning favor the surgical approach of the underlying venous change because it allows differentiation between patients with primary varicose veins, whose changes mainly occur in the superficial venous system, and patients with secondary varicose veins, in whom the deep venous system is the site of pathophysiologic changes.

The pulses of the lower limbs should be palpated, and are usually normal. A decrease in pulse or its absence should make one aware of arterial disease as a cause of ulceration or an association with venous disease, featuring in the latter case ulcers of mixed etiology (venous and arterial) [11].

Doppler ultrasonography should be used to determine systolic index between the ankle and the arm (ankle–brachial index; ABI). The index is calculated with the highest systolic blood pressure of the ankle divided by the systolic blood pressure of the brachial artery. ABI below 0.9 indicates that there is insufficient blood component influencing the development of ulcer [13].

Duplex scanning is a noninvasive method of choice to assess the superficial, deep, and perforating venous system, since the venous change may be located in the superficial, deep, or perforating veins, in isolation or combined. In addition, it provides a functional assessment to identify whether the disease is due to venous reflux, obstruction, or both [14].

Fig. 65.1 Typical venous ulcers with lipodermatosclerosis and hyperpigmentation (ochre dermatitis) in peripheral wound area

Qualitative bacteriologic tests using swabs and bacterial cultures should not be performed in a systematic way because they cannot differentiate whether there is colonization or infection [15].

Treatment

The main methods of VU treatment are compression therapy, local treatment of ulcers, systemic medications, and surgical treatment of venous abnormalities.

Compression Therapy

This approach aims to decrease chronic venous hypertension and its impact on macrocirculation and microcirculation. It is contraindicated in the presence of severe arterial disease. The most commonly used methods are compression bandages and elastic stockings.

The bandages can be inelastic and elastic [16]. Among the more traditional inelastic is Unna's boot, consisting of bandage impregnated with zinc oxide, creating a semi-solid mold for carrying out efficient external compression. The modified Unna's boot (Fig. 65.2) is less rigid and uses a small stretch bandage, for example, Viscopaste® (Smith & Nephew) and Flexdress® (ConvaTec). Both the traditional and modified Unna's boot should remain in place for 7 days, although at the beginning of treatment, when there is large amount of exudate and edema, it can be reapplied more often [17].

Elastic bandages have higher stretch and are widely used in clinical practice. An example is the Surepress® (ConvaTec). It has rectangles on the surface which turn into squares when the stretch reaches proper tension (Fig. 65.3a, b). In general it should be immediately applied when the patient wakes up and be removed at the end of the day. It can be washed but should be discarded as soon as stretch is lost.

The most effective elastic compression is performed by multilayers. With this type of compression, sustained pressure of 40–45 mmHg is achieved at the ankle. An example of this compression is Dynaflex® (Johnson & Johnson), whose first layer of wool and foam is applied in a

Fig. 65.2 Compression therapy with Unna's boot

spiral, which absorbs the exudate and redistributes the pressure around the ankle; the second layer consists of elastic compression bandage, and the third a layer of adhesive bandage which maintains all of the layers properly (Fig. 65.4a–c). This compression system may remain in place for 7 days [18].

These inelastic and elastic compression bandages may be harmful or useless if not properly used, and their effectiveness can be influenced by the application technique used by doctors, nurses, or patients themselves.

The stockings are generally difficult to use in the active phase because of the difficulty in proper placement for ulcer patients; they are most suitable for the post-healing period to avoid recurrences [19].

Ulcer Treatment

Local treatment should begin with bedside evaluation of the ulcer, which requires systematic and structured assessment in order to detect the possible factors that negatively interfere with the

Fig. 65.3 (**a**) Placement of elastic compression with the technique half and half. (**b**) Elastic band applied instep to just below the knee

healing process. To facilitate this evaluation a mnemonic rule using the acronym TIME has been created. The letter T refers to tissue, i.e., assessment for the presence of devitalized or non-viable tissue; I refers to the presence of infection or colonization; M refers to moisture imbalance; and E refers to edge of wound [20].

After this evaluation, cleansing of the ulcer is carried out. This should be performed with physiologic saline solution or tap water, since many antiseptic substances (chlorhexidine, povidone-iodine, acetic acid, sodium hypochlorite, etc.) are cytotoxic and can delay healing.

In the presence of nonviable tissue (TIME letter T) debridement is necessary, as these tissues favor infections, and do not allow the formation of good granulation tissue and proper re-epithelialization [6]. There are basically five types of debridement: autolytic, chemical, mechanical, surgical, and biological. Autolytic debridement can be achieved

with occlusive dressings, through exudate enzyme action that remains in contact with the ulcer. Examples are hydrogel dressings such as Nu-Gel®, Saf-Gel®, Duoderm Gel®, IntraSite Gel®, and Purilon® (Fig. 65.5a–c) and hydrocolloid dressings such as Nu-derm®, Tegasorb®, Comfeel®, and Duoderm® (Fig. 65.6a, b). Chemical debridement is accomplished by application of various enzymes including papain and collagenase. Mechanical debridement can be performed using surgical instruments or by the application of dressings ranging from moist to dry, but the main disadvantage is the inability to be selective when removing viable tissue along with devitalized tissue [21]. Negative pressure therapy (e.g., VAC®) is an alternative whose use has been expanding in recent years [22].

For the approach to infection or colonization of the ulcer bed (Letter I of TIME), it is essential to know the difference between colonization and

Fig. 65.4 Multilayer compression. (**a**) First layer of wool and foam applied in a spiral. (**b**) Second layer consists of elastic compression bandage. (**c**) Final layer of adhesive bandage

infection of chronic ulcers. The increased number of bacteria in the wound bed does not necessarily mean infection. Ulcer with critical colonization represents increased bacterial load, and these bacteria can form complex structures called biofilms. Biofilms are communities of microorganisms surrounded by a matrix of extracellular polysaccharides. Bacteria in biofilms are
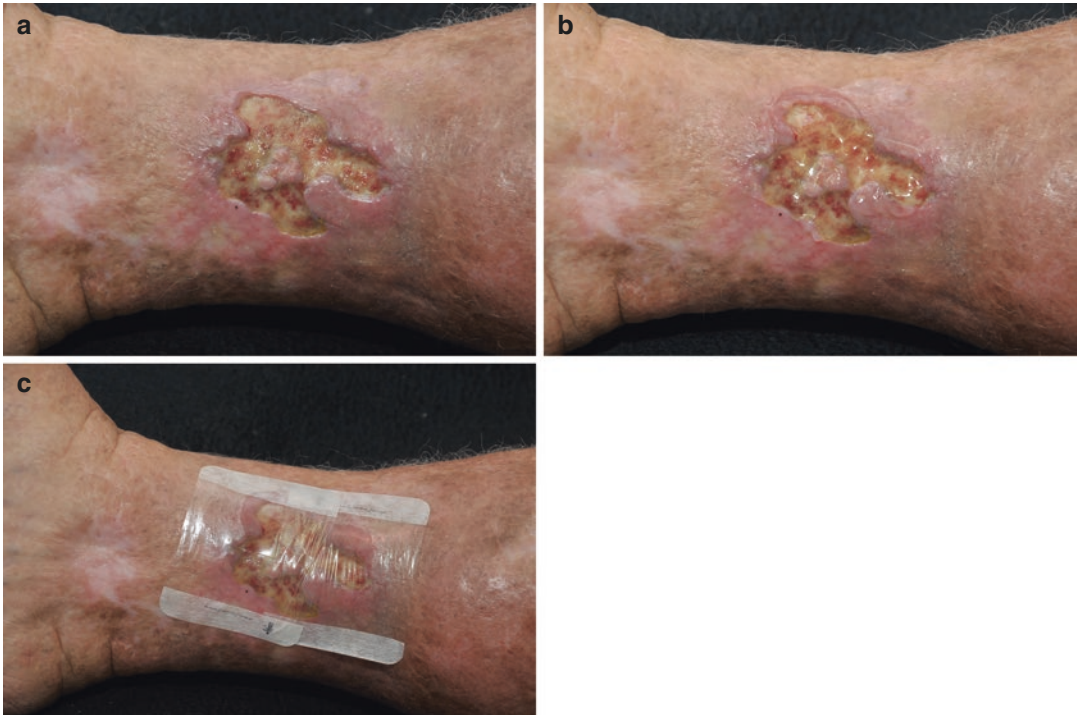
Fig. 65.5 (**a**) Venous ulcer with wound bed devitalized and little exudate. (**b**) Hydrogel in wound bed. (**c**) Secondary dressing with plastic film. This dressing can be left in this ulcer for 2–3 days

better protected and more resistant to the body's defenses, antiseptics, and antibiotics, both topical and systemic. A critically colonized ulcer does not have well granulated tissue, but friable greenish or purplish tissue (Fig. 65.7), with excessive exudation and foul odor; it does not respond to conventional treatment. However, sometimes the only sign of critical colonization is the failure to heal [23].

Local treatment of ulcers with critical colonization can be performed surgically or with chemical debridement. Occlusive dressings with hydrofiber, alginate, and silver are options that control the excess exudate and promote reduction in bacterial load (e.g., activated carbon with silver – Actisorb Plus®, with hydrofiber with silver – Aquacell prata®, alginate – Kaltostat®). These dressings can be changed, according to saturation, after 3–7 days (Fig. 65.8a, b). It must be emphasized that systemic antibiotics are not indicated for failure to act on biofilm.

Soft tissue infections occur when there is penetration of bacteria in periwound tissues, whereby erythema, edema, local heat in tissues surrounding the ulcer, and pain are evident. Treatment should be carried out with systemic antibiotics and debridement of the infected tissue when necessary.

Another important aspect is to maintain the moist environment (letter M of TIME). Excess exudate must be combated because, besides favoring infections, this brings discomfort to the patient. On the other hand, dehydration of the ulcer bed must be avoided and countered because it favors the formation of devitalized tissue. Therefore, to provide an optimal way of healing some occlusive dressings can be specified according to the characteristics of ulcers. Ulcers with excess exudate are best treated with hydrofiber dressing, alginates, carbon and silver, and carbon and alginate (Fig. 65.8). For ulcers with mild to moderate exudate, curative hydrocolloids and hydrogels are indicated (Figs. 65.5 and 65.6). Compression therapy can and should be used where possible with such dressings [6].
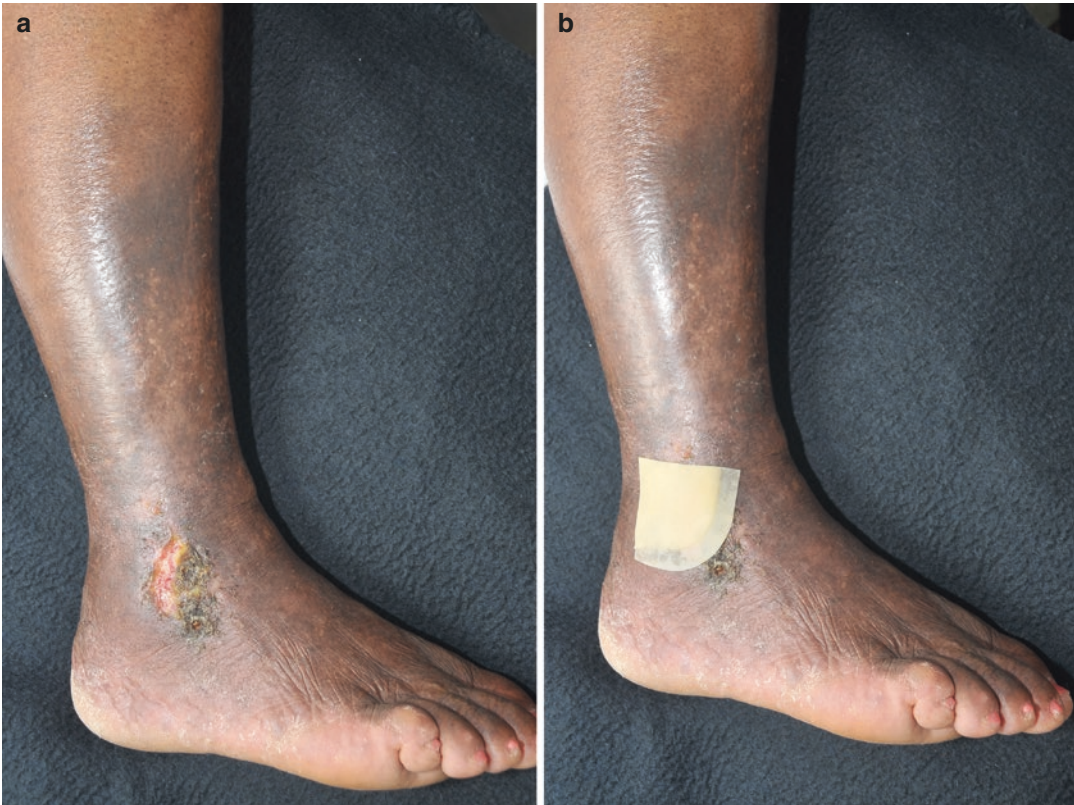
Fig. 65.6 (**a**) Venous ulcer with wound bed with little devitalized tissue and little exudate. (**b**) Hydrocolloid dressing. This dressing can be left in this ulcer for 5–7 days, according to its saturation

Fig. 65.7 Venous ulcer with critical colonization: part of the wound bed presents itself *greenish* and *grayish*, with clinical features of bacterial burden

Systemic Drug Therapy

For long-standing or large venous leg ulcer, treatment with either pentoxifylline or micronized purified flavonoid fraction used in combination with compression therapy is recommend [6].

Surgical Treatment of Venous Ulcer

Surgical correction of insufficient veins favors ulcer healing and also improves the prognosis by reducing the relapse rate. Patients who benefit most from surgical treatment are those with insufficiency of the superficial venous system, alone or combined with insufficient perforation [6].

Ancillary Measures

The remaining measures must be oriented to decrease venous hypertension. The lower limbs should be elevated above the heart level for 30 min about three to four times each day. The optimum position is achieved by raising the foot above the bed to a height ranging from 15 to 20 cm. Short walks, three to four times a day, should be encouraged. Patients should be instructed to maintain their weight within the normal range and avoid smoking. Manual lymphatic drainage and physiotherapy to improve ankle joint mobility are necessary in some patients.
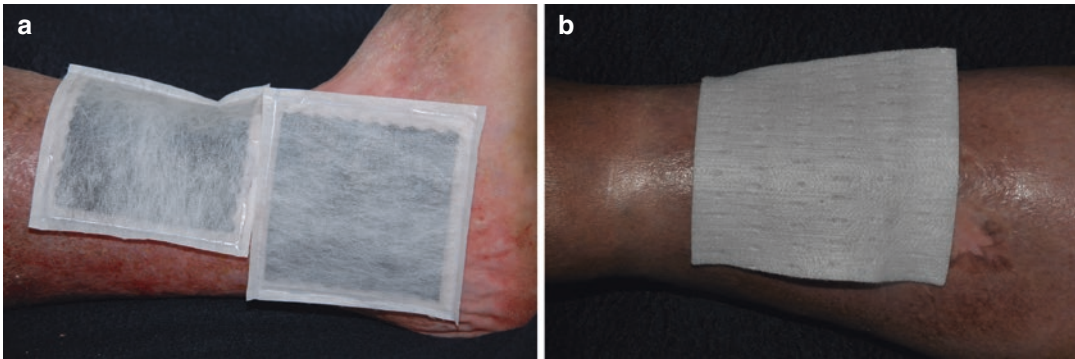
Fig. 65.8 (**a**) Dressing with activated carbon with silver. (**b**) Hydrofiber with silver. These dressings are indicated for ulcers with critical colonization and high exudation

Methods to Prevent Relapses

The rate of relapse after venous ulcer healing is very high. The most necessary measures to reduce the relapse rate are educating the patient about the use of high-compression stockings of high compression and adequate surgical intervention for venous abnormality [24].

Arterial Ulcer

Epidemiology

Arterial ulcer is the second most common cause of leg ulcers, corresponding to 10–25% of cases [25]. Risk factors for development are age over 45 years, smoking, diabetes mellitus, hyperlipidemia, hypertension, hypercholesterolemia, family history of atherosclerotic disease, and sedentary lifestyle [26].

Etiopathogenesis

The gradual narrowing of the artery lumen as a result of atherosclerotic disease causes gradual obstruction of blood flow and consequent formation of collateral circulation. The reduction in the blood supply results in ischemia, necrosis, and ulceration [27].

Clinical Presentation

The main symptom associated with arterial ulcer is intermittent claudication, i.e., pain in the calf or thigh during walking with improvement after a few minutes of rest. Pain at rest often occurs with progression of the disease, to the point of the patient having to sleep while sitting. Ulcers occur mainly on bony prominences of the feet, ankles, and heels. However they may occur in other sites, especially when initiated by trauma. They are usually deep, with well-defined and undermined edges and devitalized bed, and often necrotic (Fig. 65.9). Exposed tendons and deep tissue may occur more frequently than in venous ulcer. The periulcer area may be erythematous.

Complementary Test

The affected limb is often colder, with pallor during lifting and flushing when bending. The absence of peripheral pulses allied to the clinical manifestations described suggests arterial etiology for the ulcer. Capillary refill time is slow (more than 3–4 s), obtained by hallux compression until becoming white and then released.

Doppler ultrasonography should be used to determine the systolic index between the ankle and the arm (ABI). ABI below 0.9 indicates that there is insufficient blood component influencing the development of the ulcer. ABI below 0.7 is highly significant and, when there is no abnormal vein, can indicate that arterial insufficiency is the only cause of the ulcer. It is important to remember that the absence of distal pulses is also considered indicative of arterial disease, regardless of the value of the index [28].

Fig. 65.9 Arterial ulcers with necrosis of the wound bed and erythematous peripheral wound skin. There are no tibial or dorsal pedis pulses palpable, and ABI is <0.6

Arterial duplex scanning is important for treatment planning because it allows assessment of the distribution and extent of arterial disease [28].

Treatment

Assessment by the vascular surgeon is very important. Limbs with critical ischemia with resting pain and low blood pressure in the ankle (below 50 mmHg) may benefit from bypass surgery or angioplasty, or often a combination of both procedures. If the patient has no clinical indication for the procedure or the prospects of improvement with revascularization are poor, amputation should be considered. Drug treatment includes aspirin (due to antiplatelet action), clopidogrel (inhibitor of ADP-inducing platelet aggregation), and cilostazol (phosphodiesterase III inhibitor) [29].

Local treatment of the ulcer is aimed at maintaining wound moisture. Additional therapies include adequate pain control and maintenance of the affected limb.

Neuropathic Ulcers

Neuropathic ulcers occur as a result of sensory loss and trophic changes due to denervation [30]. Among the many causes of peripheral sensory neuropathy in Western countries, the main ones are diabetes mellitus, leprosy, spina bifida, spinal cord injuries, alcohol, drugs, and hereditary sensory and motor neuropathies. Whatever the cause, sensory loss in the feet puts them at risk when traumatized. Ulcers on the feet are the most common cause of hospitalization of diabetic patients from Western countries.

Etiopathogenesis

The two main causes of peripheral neuropathy and neuropathic ulcers are diabetes mellitus and leprosy. Diabetic neuropathy is a chronic, insidious, sensory neuropathy, which also encompasses motor and autonomic neuropathy. The feet lose their sensitivity and therefore may be under pressure. The motor change causes atrophy with change in the intrinsic muscles of the feet, which leads to deformities with increased load, mainly at the base of the metatarsals. Autonomic dysfunction results in dry skin, which is more prone to infections and eczema. This dysfunction also causes changes in the microcirculatory blood flow through interference in arteriovenous shunts. All of these changes lead to the appearance of ulcers especially in the plantar region of diabetic patients, known as perforating plantar ulcers [31].

In leprosy, *Mycobacterium leprae* has particular tropism for peripheral nerves. The lesions in nerve fibers are essentially sensory, motor, and autonomic. In the lower limbs the main nerves affected are the peroneal and posterior tibial. The fibula, when injured, causes "foot drop" and loss of sensation on the dorsum of the feet and outward side of the leg. Lesions of the posterior tibial nerve lead to paralysis of the intrinsic muscles of the foot, hypoesthesia, or anesthesia. Sensory and motor changes are responsible for the pathogenesis of perforating plantar ulcer [32].

Clinical Presentation

Perforating plantar ulcer is the typical sign of diabetic and leprosy neuropathy. It is characterized by a painless ulcer with deep and calloused edges (Fig. 65.10).

Neuropathic ulcers may occur in other locations, particularly in those subject to trauma. Irregularities in the inner linings of shoes or foreign materials such as small stones may go unnoticed and cause ulcers. Osteomyelitis and bacterial soft tissue infections are frequent complications.

Fig. 65.10 Perforating plantar ulcer in patients with diabetes mellitus with important deformities of feet

Complementary Test

The test of Semmes–Weinstein is used to test the perception of pressure. If the patient is unable to detect the test when using monofilaments 5.07 (10 g) in the plantar region, this is considered as loss of protective sensation, and therefore an increased risk for ulceration in regions with such presentation [33].

It is necessary to conduct serial radiographs to assess the bone, especially in the case of deep ulcers that affect the bones. Other tests may be needed to confirm osteomyelitis, such as magnetic resonance imaging and bone scintigraphy.

Treatment

The management of patients with peripheral neuropathy should be in three dimensions: preventive, local treatment of ulcer, and measures to reduce plantar pressure.

The basic preventive measures are: orientation in relation to shoes, particularly new shoes, with special attention to the seams and maladjustments; guidance for use of insoles that distribute the weight in the plantar region to reduce high pressure; patients and caregivers should make systematic inspection of the feet looking for initial areas of trauma such as erythema and blisters; in cases of dry skin it is essential to use lotions to prevent fissures; it is important to advise patients not to walk barefoot; guidance regarding weight loss should be provided for overweight and obese patients.

The approach to the treatment of ulcer is as follows. When the ulcer is infectious it requires appropriate systemic antibiotics; in the case of critical colonization, topical antibiotics can be used for reduction of bacterial flora in the granulation tissue, but for short periods, to avoid cytotoxic effects and resistance; dressings such as hydrofiber, activated carbon, and silver are indicated. If there is no critical colonization and infection, dressings such as hydrocolloids and hydrogels may be indicated to maintain the moist environment and debridement autolysis. Chemical or surgical debridement of devitalized tissue and callous tissue of the ulcer edges should be made whenever necessary. The selected dressing should also maintain moisture balance and avoid excess exudate, which promotes skin maceration around the ulcer, favoring an increase in the ulcerated lesion and slowing the healing process [34].

Pressure relief, or off-loading, is another key aspect in these patients. Measures to achieve this goal are: orthoses that promote the reduction of pressure on the ulcerated sites and calluses; in cases of major orthopedic deformities, specially made shoes customized to allow greater width and depth; crutches and walkers; and even total deprivation of contact. The choice of off-loading modality should be determined by the patient's physical characteristics and the ability to comply with treatment, as well as by the location and severity of the ulcer [34].

In the case of osteomyelitis, treatment consists in removal of infected bone, accompanied by 2–4 weeks of systemic antibiotics. However, when this is not possible, antibiotics should be prescribed for long periods [35].

Less Common Causes of Chronic Leg Ulcers

Hypertensive Ischemic Ulcer (Martorell Ulcer)

Hypertensive ischemic ulcer is a rapidly progressive and extremely painful ulcer that is frequently underdiagnosed, and which should not be confused with arterial ulcers. In arterial ulcer there is involvement of micro- and macrocirculation, whereas a hypertensive ulcer involves only the microcirculation. Failure of vasodilation in response to arteriolar narrowing caused by hypertension determines the reduction of skin perfusion that results in formation of a hypertensive ischemic ulcer. The physiopathology of an arterial ulcer is different because here the reduction in skin perfusion pressure is due to reduction of the arterial flow in the macrocirculation [36].

It occurs in patients with arterial hypertension that is difficult to control, and was first described by Martorell, Hines, and Farber in the 1940s. These ulcers occur most commonly in women, especially after the sixth decade.

Clinical Presentation

These ulcers often are located in the anterolateral and posterior portions of the legs and may have purplish color or be erythematous in the periulcer region (Fig. 65.11). In general they are very painful disproportionately to the size of the ulcer and are often refractory to standard therapy for chronic ulcers [37]. Peripheral pulses are palpable, and ABI is greater than 0.9 [36].

Treatment

Hypertensive ulcers do not respond to local treatment. The reduction and control of blood pressure is the best therapeutic measure. The most commonly used antihypertensive drugs are calcium channel blockers and angiotensin-converting enzyme inhibitors. Many patients with hypertensive ulcer use
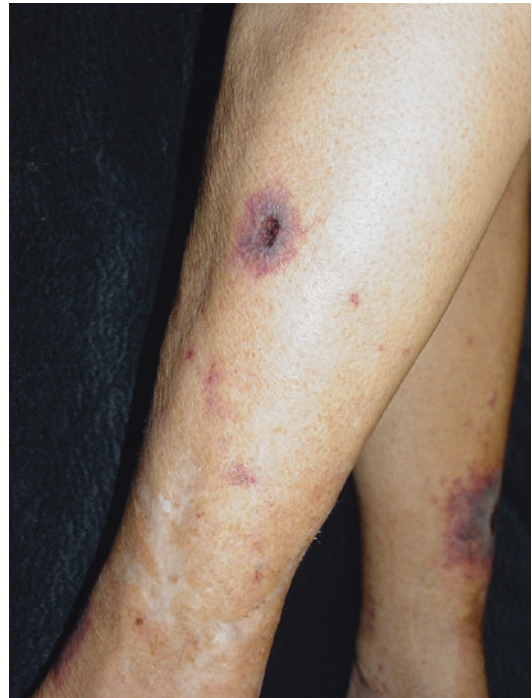
Fig. 65.11 Woman with severe hypertension and sudden onset of painful hypertensive leg ulcers. Palpable peripheral pulses and ABI = 1.0

β-blockers for blood pressure control, but these should be replaced with other antihypertensive classes since they may aggravate vasoconstriction and therefore impair healing [38].

Pyoderma Gangrenosum

Pyoderma gangrenosum is a rare, ulcerative, cutaneous condition. First described in 1930, the pathogenesis of pyoderma gangrenosum remains unknown, but is probably related to a hyperergic reaction and is considered an inflammatory ulcer. Usually the disease begins as a papule, vesicle, or pustules that quickly ulcerate, generating a very painful injury. It occurs most often in lower limbs but can occur elsewhere. It usually is necrotic with purpura and undermined borders (Fig. 65.12). It is frequently associated with systemic diseases such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, and myeloproliferative diseases [39].

The treatment is mainly systemic corticosteroids (1 mg/kg). Local care of the ulcer is important. In the initial phase, which can involve critical colonization

Fig. 65.12 Pyoderma gangrenous on the side of the leg. Ulcer with infiltrated and purplish edge

and exudation, the use of dressings with activated carbon/silver or hydrofiber with silver and alginates, with changes every 3 days, is recommended. In the following stages, hydrogels and hydrocolloid dressings promote autolytic debridement and accelerate healing. Surgical debridement should be avoided because of the pathergy phenomenon, i.e., onset or worsening of injury by trauma [40].

Leg Ulcers in Rheumatoid Arthritis

Ulcers associated with rheumatoid arthritis may occur in the lower limbs and are multifactorial. Many are due to chronic venous insufficiency, because patients have deformities in the regions of the ankle, worsening function of the calf muscle pump via difficulty in dorsiflexion, and therefore have similar venous ulcers (Fig. 65.13). Less often the ulcer is associated with vasculitis disease activity with high titers of rheumatoid factor. Pyoderma gangrenosum is another possible consequence of chronic ulcers of the lower limbs in patients with rheumatoid arthritis [40].

Treatment is a challenge and depends on the main cause of the ulcer. Elastic compression with an Unna's boot is useful since it is often associated with venous insufficiency. Local care of the ulcer is also very important and follows the principles of treatment of venous ulcers previously described.

Fig. 65.13 Chronic ulcers in patients with rheumatoid arthritis with deformities in the feet and joints

Leg Ulcers due to Vasculitis

Vasculitis of small and medium vessels can result in leg skin ulcerations. They begin with purpuric and necrotic areas that later progress to ulceration. Examples include leukocytoclastic vasculitis (Fig. 65.14), cryoglobulinemia, Henoch–Schönlein purpura, polyarteritis nodosa, Churg–Strauss syndrome, and Wegener's granulomatosis [40].

Leg Ulcers due to Thrombophilia

Thrombophilia is defined as abnormalities in the blood coagulation and/or the fibrinolytic cascade leading to hypercoagulability states. It can be inherited or acquired and predisposes to venous and/or arterial thrombosis at relatively young ages.

Thrombophilia can cause ulcers in the lower limbs indirectly as a result of deep vein thrombosis, or directly through the formation of thrombi

Fig. 65.14 Livedoid vasculopathy characterized by small and superficial ulcers. There are also purple macules and porcelain-white, atrophic plaques

in arteries, arterioles, capillaries, and venules. Microthrombotic ulcers are characterized by pain, gangrene, and lower limb ischemia, preceded by livedo reticular and white atrophy. Usually the feet are warm and distal pulses are palpable [40].

The antiphospholipid syndrome is the main condition of acquired blood hypercoagulability. Patients may have a history of cerebrovascular accident, myocardial infarction, deep vein thrombosis, recurrent fetal loss, and pulmonary thromboembolism. Treatment is aimed at control of thromboembolic events with anticoagulants and antiplatelet agents. [41]

Livedoid Vasculopathy

Livedoid vasculopathy occurs mainly in middle-aged women. It is involved in the pathogenesis local or systemic coagulation changes leading to the formation of fibrin thrombi in the dermal vessels. In general, there is formation of small and recurrent ulcers in the leg, characterized by painful purple macules and papules that subsequently ulcerate. The ulcers heal over weeks to months resulting in smooth, porcelain-white, atrophic plaque-like areas with surrounding telangiectasia and hyperpigmentation (Fig. 65.14) [42].

Treatment is a real challenge and many therapies are cited in the literature. The treatment is based on the use of anticoagulants such as warfarin (especially when associated with antiphospholipid syndrome, factor V Leiden), antiplatelet agents (aspirin, dipyridamole), pentoxifylline, danazol, and other fibrinolytic agents. Other therapies described include the use of niacin, psoralen combined with ultraviolet A, and intravenous immunoglobulins. Additional measures such as rest and compression therapy are also important [43].

Leg Ulcers Associated with Hematologic Diseases

Some hematologic diseases such as sickle cell anemia, thalassemia, thrombotic thrombocytosis, and polycythemia vera are responsible for chronic leg ulcers. In most cases, ulcers develop secondary to deep venous thrombosis and capillary thrombosis [1].

Leg Ulcer due to Infections

Infectious diseases such as cutaneous leishmaniasis and paracoccidioidomycosis can cause chronic ulcers of the lower limbs. The ulcers of leishmaniasis usually are circular, with infiltrated borders and granular clean wound beds (Fig. 65.15). The ulcer in paracoccidioidomycosis may have a wound bed with hemorrhagic dotted appearance (Fig. 65.16). The diagnosis should be based on clinical, epidemiologic, and laboratory abnormalities.

Leg Ulcer of Neoplastic Origin

Squamous cell carcinoma, basal cell carcinoma, and lymphomas may present as chronic leg ulcers and are therefore primary neoplastic ulcers [44]. Another situation is neoplastic transformation of chronic ulcers such as in long-term venous ulcers, which may undergo malignant transformation into squamous or basal cell carcinoma; these are called Marjolin's ulcers (Fig. 65.15). In the latter situation, in general the tumor begins at the edge of the ulcer or scar and grows slowly and only a portion of the ulcer suffers malignant transformation, increasing the chance of false-negative histopathology. To confirm the diagnosis of suspicious lesions multiple biopsies should be performed, preferably

Fig. 65.15 Neoplastic transformation of chronic venous ulcers to squamous cell carcinoma (Marjolin's ulcer). Hypertrophy of granulation tissue is noticeable

Fig. 65.16 Chronic bilateral lymphedema of lower limbs

in the edges of the lesion. Treatment should be complete excision of the tumor with adequate surgical margins and subsequent reconstruction with grafts and skin flaps. Limb amputation is indicated in cases of extensive invasion of local tissues and involvement of the joint or bone [45].

Leg Ulcer due to Lymphedema

This is rare when not associated with venous insufficiency. Injuries and subsequent infections can lead to formation of ulcers. Treatment is based on local care of the ulcer and compression therapy.

Other Causes of Chronic Leg Ulcers

Other rare causes of chronic leg ulcers are the drugs warfarin and hydroxyurea, as they may cause vascular occlusion with subsequent formation of ulcers in the legs; necrobiosis lipoidica, ulcers as manifestations of microvascular occlusion syndromes, cryoglobulins, cryofibrinogen, vascular occlusion by cholesterol emboli and oxalate, calciphylaxis, vascular coagulopathy (Sneddon syndrome), and vascular invasion by microorganisms (ecthyma gangrenosum, opportunistic fungi, Lucio phenomenon (in leprosy)).

Lymphedema

Lymphedema is defined as a functional or anatomic disorder of the lymphatic system that causes accumulation of protein-rich fluid and subsequent inflammation, adipose tissue hypertrophy, and fibrosis. As lymphatic drainage accounts for 1–10% of interstitial drainage, most lymphedemas have a chronic and progressive course, and adequate treatment rarely improves it but lengthens this progression [46, 47].

There are congenital (primary) and acquired (secondary) causes of lymphedema (Chart 65.3). Nevertheless, the progressive swelling and skin induration inflict limitations on mobility and function that favor recurrent infection and skin ulcers, and significantly decrease overall quality of life [46, 48].

The real prevalence of lymphedema per se is not known and varies according to the causes and

Chart 65.3 Main causes of lymphedema

Primary lymphedema	Milroy's disease Meige's disease Amniotic band Proteus syndrome Yellow nail syndrome Neurofibromatosis Vascular malformation
Secondary lymphedema	Wuchereriosis Soft tissue infection (erysipelas) Trauma Obesity Neoplastic obstruction (lymphangitis, external compression, or lymphatic metastasis) Iatrogenic (lymphadenectomy or lymphatic resection/transection) Radiotherapy Podoconiosis

population of study. The rates of arm lymphedema after mastectomy range from 4% to 50% according to the surgical technique. Acquired lymphedema and the association with venous insufficiency is the most prominent picture. In a British community, the overall prevalence was about 0.01% of the population, with a predominance of older women. Primary lymphedema is extremely rare [46, 49].

The clinical presentation of lymphedema can vary according to the cause, severity, and topography. Adequate anamnesis should be taken to characterize the evolution time, familiar occurrence, and precipitating factors such as infection, trauma, surgical procedure, radiotherapy, weight gain, and malignancy.

Initial (Stage 0), swelling is not clinically evident, merely the lymphatic transportation being impaired. At Stage I there is mild, pitting edema that resolves with limb elevation. In a later Stage II, pitting is not present and swelling does not revert with limb elevation. At Stage III there is a patent skin induration with lymphostatic elephantiasis, and pitting is absent. Trophic skin changes, such as acanthosis, fat deposits, and warty overgrowths (mossy foot), are noticeable (Figs. 65.16, 65.17, and 65.18). On the lower limbs the Kaposi–Stemmer sign – digital pinch at the base of the second toe – is usually present, and complications such as ulcers and chronic lipodermosclerosis can arise [46, 50].

Fig. 65.17 Chronic ulcer in a lymphedematous limb

In general, the diagnosis of lymphedema occurs frequently at later stages (Stage II or III) because mild swelling is generally asymptomatic. There is usually no great difficulty in establishing the diagnosis after clinical examination, but computed tomography and lymphoscintigraphy can help in the confirmation of lymph node stasis.

Despite its rarity, clinicians should be aware that chronic lymphedema is associated with the development of lymphangiosarcoma (e.g., Stewart–Treves syndrome), Kaposi sarcoma, or lymphoma [51].

Postoperative or post-trauma lymphedema should be treated with precocious lymphatic drainage, elevated limb at rest, and compression stockings.

A multidisciplinary team that includes a vascular surgeon, physiotherapist, nurse, and dermatologist should manage chronic lymphedema.

Conservative treatment with compression is the first option for mild to moderate cases. Multilayer inelastic band or controlled compression therapy reduces the edema volume in up to 46% of cases. Additional physical therapy (e.g., lymphatic drainage and exercises) are recommended.

Diuretics and benzopyrones are prescribed in selected cases. Surgical therapy is effective in decompression (debulking of the compressive

Fig. 65.18 Hypertrophic acral papillomatosis due to chronic lymphedema, leading to a mossy foot appearance

tissue and liposuction). Microsurgery (lympho-venous anastomosis) is not widely performed, and the results are as favorable as those for compressive regimens. The recommendation for amputation in severe cases and multiple complications due to lymphedema should be discussed with patients.

Areas with lymphedema should be protected from trauma, burn, and venipuncture; moreover, patients should be made aware of adequate moisturizing and cautionary nail care without pushing back cuticles. All patients with chronic lymphedema benefit from 1,200,000 IU penicillin, intramuscularly, every 3 weeks for prevention of soft tissue infection [52].

Glossary

Lipodermosclerosis Considered a type of panniculitis (inflammation of subcutaneous fat). Literally means "scarring of the skin and fat" and is a slow process that occurs over a number of years. It is a condition that affects the skin just above the ankle in patients with long-standing venous disease resulting in chronic venous insufficiency. The end result of untreated lipodermosclerosis is ulcer formation with high incidence of delayed healing and infection.

Lymphedema An abnormal collection of high-protein fluid just beneath the skin. It usually develops when lymph vessels are damaged or lymph nodes are removed (secondary lymphedema) but can also be present when lymphatic vessels are missing or impaired due to a hereditary condition (primary lymphedema).

Vasculitis Inflammation of the blood vessels. It causes changes in the walls of blood vessels, including thickening, weakening, narrowing, and scarring. These changes restrict blood flow, resulting in organ and tissue damage.

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Xerosis

Clarice Gabardo Ritter

Key Points
- Xerosis is a very common disorder in the general population
- Dry skin can be caused or aggravated by factors such as age, associated dermatosis, genetic background, and environmental factors
- Moisturizers are effective in reducing dry skin symptoms

Abbreviations

AD   Atopic dermatitis
NMF   Natural moisturizing factor
SC   Stratum corneum
TEWL   Transepidermal water loss

Introduction

Xerosis, or dry skin, is a cutaneous reaction indicative of abnormal desquamation resulting in a rough texture and appearance of the skin. Skin becomes dehydrated when the stratum corneum (SC) is unable to retain water and loses moisture faster than it is replenished. It is a very common condition among the general population, especially the elderly, in whom the prevalence can reach from 30% to 60% [1–3]. Dry skin can occur in association with many other dermatoses and unfavorable environmental factors.

Dry skin can affect the patient's quality of life and work productivity because it can cause discomfort, pain, and itching, and repetitive scratching can result in secondary lesions. Severe xerosis can lead to the onset of a type of eczema characterized by intensely itchy, fissured, and cracked skin called xerotic eczema or eczema craquelé.

Emollients are central to the management of xerosis, and the aim of treatment with emollients is primarily to restore epidermal differentiation, leading to the restoration of normal skin. However, dry skin is often the result of a combination of etiologic factors, so the treatment involves multiple actions, such as bath and soap care and control of other environmental factors.

State of the Art

Besides xerosis being a common symptom of a great number of skin conditions, only fairly recently has more progress been made toward elucidating the structure and function of the SC and the mechanisms that result in xerosis.

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Nowadays we have a better understanding of the complex pathophysiology of epidermis and SC, and it is believed that disturbed epidermal differentiation is a root cause of dry skin [4]. The disturbance of epidermal differentiation can include a wide range of etiologic factors that often work together, such as genetic background, metabolic causes, and environmental triggers.

The treatment of xerosis with emollients has scientific evidence of efficacy. This approach can prevent flares of atopic dermatitis and psoriasis, and manifest anti-inflammatory properties, and it can improve patients' quality of life and reduce prescription costs [5].

The traditional use of simple emollients using nonphysiologic lipids such as petrolatum and mineral oil create a fine occlusive layer, thereby reducing water loss from the SC. Current knowledge supports the use of additional ingredients, such as humectants and physiologic lipids, which rapidly penetrate the epidermis and have more physiologic actions to restore epidermal differentiation [4, 5].

A recent systematic review about skin care in the aged demonstrated that application of moisturizers containing humectants such as lactic acid, urea, glycerin, and α-hydroxy acids is clearly effective in reducing dry skin conditions and enhancing the skin barrier function. However, there is no evidence that one humectant-containing moisturizer is superior to another [6].

Pathogenesis of Dry Skin

The epidermis is a stratified keratinized epithelium and is the main affected skin layer in the xerosis process. The most important function of the epidermis lies in the SC, a cornified layer of epidermis that provides physical protection against water loss and prevents the passage of soluble substances into the body from outside.

The principal acellular components of the SC are the structural proteins, the intercellular lipids, the natural moisturizing factor (NMF), and the enzyme systems. The success in maintaining epidermal homeostasis depends on coordinate actions between these elements. Epidermal

enzyme activity promotes synthesis of lipids and the subsequent degradation of intercellular bonds to produce physiologic desquamation. This enzymatic activity is modulated by several factors including pH, temperature, and hydration. If, for some reason, a decrease in lipid content occurs, there will be an increase in insensible transepidermal water loss (TEWL), which in turn will destabilize the optimum environment for epidermal enzyme activity. These events will culminate in a disruption of the process of corneocyte maturation and inhibition of cell desquamation in a self-perpetuating cycle of dry skin. In summary, xerosis is the result of an impairment of epidermal desquamation [4, 7].

The barrier function and skin hydration depend on two essential elements: the lipids present in the SC and the levels of NMF. The lipids are formed on stratum granulosum and then migrate upward into the SC during the process of epidermal differentiation. Their intercellular component is arranged in bilayers between the corneocytes. Through an enzymatic process, these lipids are transformed on nonpolar lipids such as ceramides, free fatty acids, and cholesterol. A lipid deficiency destabilizes SC hydration, affecting the elasticity and flexibility of healthy skin [8].

The NMF is a water-retaining substance, composed of a mixture of amino acids and salts generated by filaggrin hydrolysis. This substance is highly water soluble and has great water-retention capacity. It is responsible for retaining the turgidity of corneocytes and preventing skin cracking and desquamation. The water content of a healthy SC under normal conditions is 15–20% [9]. When the water content of the cornified layer falls below 10%, visible scales form and the skin acquires a rough, dry appearance.

Aquaporin-3, an epidermal water/glycerol transporter, is also the subject of recent studies about the pathogenesis of xerosis. These channels are responsible for carrying glycerol into the SC, where it acts as an endogenous humectant. The expression of the aquaporin-3 in human skin is strongly affected by aging and chronic sun exposure. The high prevalence of xerosis in these clinical situations may be justified by the lower levels of these channels [4].

The SC contains other moisturizing components, such as hyaluronic acid and lactate. These components also play a role in maintaining the physical properties of the epithelial barrier [10].

Epidemiology and Clinical Aspects of Xerosis

Most people have experienced xerosis, a very common skin condition, at some point in their lives. The available epidemiologic data are generally related to elderly patients. One study of community-dwelling individuals found prevalence as high as 38.9% [11], and a recent cross-sectional study in a primary care setting showed that in patients >65 years 56% experienced at least some degree of xerosis [3]. Other long-term care studies found prevalence to range from 29.5% to 58.3% [12–14].

A physical examination will reveal rough, dry skin to the touch. There may be scaling, dry white patches, flakes, and even fissures. If the xerosis worsens, there may be redness and cracking (eczema craquelé) (Fig. 66.1), and severe cases may appear ichthyotic or fish-scale like (Fig. 66.2). The patient may complain of a

Fig. 66.2 Severe xerosis in a critically ill patient

feeling of uncomfortably tight skin and of symptoms such as itch, pain, stinging, or tingles.

Pruritus is an important clinical condition related to xerosis. The prevalence of pruritus in the elderly can be as high as 40% [11], and xerosis is the most common cause of pruritus in older adults [15]. Scratching the skin can lead to complications such as secondary infection or ulceration and chronic wounds. Managing dry skin and maintaining moisture is of utmost importance to prevent these complications.

Skin Diseases and Conditions Related to Xerosis

Dry skin is often the result of a combination of etiologic factors (Table 66.1), in particular genetic abnormalities, but also metabolic and environmental triggers. The following are the most important situations in which dry skin may be a result or a symptom.

Environmental Humidity and Temperature

It is broadly accepted that skin barrier functions may be negatively affected by climatic conditions [16]. A recent systematic review studied the neg-

Fig. 66.1 Eczema craquelé: severe xerosis with fissures and erythema

Table 66.1 Factors that contribute to xerosis

Genetic predisposition
Age
Concomitant skin diseases: atopic dermatitis, ichthyosis, psoriasis, chronic hand eczema
Comorbid diseases: hypothyroidism, diabetes, nutritional deficiency, renal disease
Medications: statins, diuretics, retinoids, targeted anticancer therapies
Environmental conditions: temperature, humidity, exposure to sunlight
Exposure to chemical agents: soaps and detergents, lotions, and perfumes
Physical insult: friction, abrasion, and radiation

ative effects of low humidity, low temperatures, and different seasons on the skin barrier and on the risk of dermatitis [17].

Meta-analysis of 99 selected studies concluded that low humidity and low temperatures lead to a general decrease in skin barrier function and increased susceptibility toward mechanical stress. As proinflammatory cytokines and cortisol are released by keratinocytes and the number of dermal mast cells increases, the skin also becomes more reactive toward skin irritants and allergens [17].

Human skin that is exposed to low relative humidity (32%) appears to be more susceptible to mechanical stress and fracture than skin in high relative humidity (96%). The exposure of healthy volunteers to very low humidity (10%) causes a decrease in skin hydration and clinically drier skin [18]. Furthermore, on experimental studies of the effect of air humidification, participants reported significantly fewer skin symptoms under higher absolute and relative humidity [19, 20]. Optimal relative humidity for lipids and protein organization is 60% [21].

The effects of cold temperature and the resulting winter xerosis have been investigated by several studies, which have identified a decrease in SC lipids and NMFs components, and an increase in SC pH and stiffness during winter [9, 22–24]. Drier skin and increased reaction to skin irritants suggest that the skin becomes more fragile and permeable in winter. The warm dry air produced by central heating systems aggravates winter xerosis [4].

Surfactant-Related Xerosis

In daily life, substances that include chemicals such as surfactants and solvents potentially perturb the SC barrier. Certain anionic surfactants such as sodium lauryl sulfate affect not only the barrier itself but also the underlying viable cell layers. For instance, sodium dodecyl sulfate upregulates intercellular adhesion molecules or vascular endothelial growth factor, suggesting that this class of surfactant has an intrinsic ability to induce epidermal hyperplasia and irritation [25, 26].

Aging

Some epidemiologic studies estimate that generalized and diffused xerosis affects between 30% and 60% of individuals over 65 years of age and is the most common cause of itching in this age group [27–29]. A history of atopy, especially atopic dermatitis, is associated with an increased risk of xerosis in the elderly [3].

There are many possible causes of dry skin in older people: a lower rate of epidermal proliferation than in a younger healthier skin, a decline in gonadal and adrenal androgens associated with decreased synthesis of sebum and ceramides, and lower levels of filaggrin, the protein from which the components of NMF are derived [7, 30]. These progressive intrinsic changes of aged skin combine synergistically with cumulative environment insults to produce structural and functional disturbances causing xerosis.

Atopic Dermatitis

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by recurrent eczema and severe pruritus. It is a multifactorial condition associated with genetic abnormalities and environmental conditions that give rise to immunologic imbalance and skin disturbances. Xerosis is almost a rule in AD, and the skin of patients with atopic eczema is characterized by low ceramide levels [31], increased transepidermal water loss [32] and decreased water-binding capacity [33].

Xerosis is such an important feature of AD that it is one of the diagnostic criteria for this dermatosis [34]. Researchers have discussed whether

xerosis is secondary to skin inflammation or if skin barrier abnormalities occur first, causing increased allergen sensitization through an impaired skin barrier and creating the conditions leading to the development of AD. Generalized xerosis, whether acquired or inherited, is also associated with other common skin disorders such as hand eczema, contact sensitization, and even asthma [35, 36].

In young children with AD, treating xerosis improves quality of life [37], decreases the risk of developing percutaneous sensitization [38] and improves AD as demonstrated by a decrease in objective AD scores [39]. In addition, a number of clinical trials have shown that treating xerosis decreases symptoms and signs of AD, including pruritus, erythema, fissuring, and lichenification [40–42]. The correct use of moisturizers can reduce inflammation and AD severity.

Ichthyosis

Ichthyosis belongs to a large group of genetic skin disorders characterized by xerosis caused by defects in the formation and function of the epithelial barrier.

Ichthyosis vulgaris is the most prevalent form of the disease (prevalence 1 in 100), and is characterized by abnormalities in the formation of keratohyalin granules and, consequently, in filaggrin. This abnormality leads to the formation of an SC deficient in many of the components of NMF. Impaired corneodesmolysis caused by defective water binding in the SC and alterations in skin pH give rise to visibly abnormal desquamation [7, 43].

Systemic Diseases and Drugs

The presence of some concomitant disease states, therapies, and medications makes individuals more susceptible to xerosis. Some of these pre-existing situations include radiation, end-stage renal disease, nutritional deficiency (especially zinc and essential fatty acids), thyroid disease, neurologic disorders with decreased sweating, HIV (human immunodeficiency virus), and malignancies. Xerosis is one of the earliest and most common signs of diabetes and is found in up to 22% of patients with type 1 diabetes mellitus [44].

Certain medications can exacerbate xerosis or eczema by interfering with skin barrier function. For example, HMG-CoA reductase inhibitors (statins) have been demonstrated to promote xerosis cutis mimicking asteatotic irritant dermatitis. Barrier dysfunction in this case is believed to be a consequence of inhibition of cholesterol biosynthesis and the resultant decrease in the production and distribution of lipids in the skin that are essential for maintaining the barrier [45, 46].

Many targeted therapies used in the treatment of some cancers can lead to the development of xerosis, and this is an important side effect of this type of therapy [47].

Other medications associated with xerosis include diuretics, antiandrogenic therapies, and retinoids [14].

Treatment

Prevention

A recent insight in the treatment of dry skin is the importance of prophylaxis between episodes of xerosis. It is suggested that preventive strategies be practiced in situations that potentially lead to dry skin, such as patients with atopic dermatitis, those with occupational contact dermatitis, and the elderly. Prevention or treatment of xerosis follows the same principles: avoidance of aggravating factors, epidermal hydration, and repair of the barrier function. Studies suggest that the skin barrier and integrity can be improved by using low-irritation cleansing products and humectant-containing moisturizers, stressing that these are the main preventive measures [6].

General Measures

Many general measures can be used to improve xerosis (Table 66.2), and consist in altering ambient humidity, changing bathing habits, and applying emollients.

As described earlier, ambient humidity can play an important role in xerosis severity. Humidity levels of less than 10% cause the SC to lose moisture, and the use of humidifier with a setting of 45–60% humid air output can prevent this occurrence.

Table 66.2 General recommendations for skin care in xerosis

Reduce the frequency and duration of bathing and use warm (not hot) water
Minimize the use of soap and use a nonirritating soap
Avoid harsh skin cleansers and powders that act as drying agents
Apply moisturizers directly to skin that is still damp
Consider using a humidifier during the winter to ensure a relative humidity setting of 45–60%
Avoid friction from washcloths, rough clothing, and abrasives

Table 66.3 Ingredients used on emollients

Ingredient	Action
Lipids (e.g., mineral, vegetable oil)	Replace the lost natural skin lipids
Physiologic lipids (e.g., ceramides, cholesterol)	Epidermal differentiation and repair of structural elements in the SC
Humectants (e.g., glycerol, urea, lactic acid)	Balance the water content of SC and restore barrier function
Antipruritic agents (e.g., glycine)	Break the itch-scratch cycle
Others (e.g., dexpanthenol)	Fibroblast proliferation and migration, epidermal differentiation

When treating patients with xerosis, it is very important to spend a long time discussing bathing habits. Water, soap, and detergent skin-washing liquids are generally the most common irritants applied to the skin. When xerosis is accompanied by itching, the application of water gives temporary relief and reduces the feeling of dryness. Therefore, it is important to convince patients to reduce excess contact with water that, in the long term, is damaging to the skin.

Topical Treatment

Emollients are essential to the management of xerosis and should be used by all patients suffering from dry skin. The aim of treatment with emollients is primarily to restore epidermal differentiation, leading to the production of normal skin. Secondly, emollient therapy should also aim to soothe the affected skin, help break the itch-and-scratch cycle, and thus prevent further physical damage to skin.

An ideal emollient should contain a combination of ingredients (Table 66.3) to protect the skin from further damage by reducing TEWL, irritation, and itching, and stimulate the production of normal skin by restoring epidermal differentiation [5]. Among these possible ingredients are occlusive lipids, physiologic lipids, humectants, and antipruritic agents.

Application of lipids to the skin surface produces skin hydration by several mechanisms, the most conventional of which is occlusion, which implies a simple reduction of the loss of water from the outside of the skin. Examples of lipids with these properties are petrolatum, lanolin, and mineral oil.

On the other hand, physiologic lipids such as ceramides, cholesterol, and free fatty acids, naturally found in the SC, seem to replenish and restore the intercellular lipid matrix [48, 49]. The application of physiologic lipids has been suggested to be more efficient compared with nonphysiologic molecules because they penetrate the SC more easily, function as structural elements in the epidermal barrier, and restore proper epidermal differentiation. However, trials between specific moisturizing products are few in number, and until now there has been no evidence of the superiority of physiologic lipids over traditional emollients [50].

Humectants, such as urea, lactic acid, and glycerol, attract and hold water in the SC, and therefore compensate for the reduced levels of NMF and other natural humectants in skin [51–53]. Applications of urea with concentrations up to 10% and lactic acid 5% reduced skin dryness, increased SC hydration, and decreased transepidermal water loss (TEWL) compared with lotions containing no humectant or no treatment [4, 5]. Based on substantial evidence, the use of emollients combined with humectants seems to be the best strategy for treating xerosis.

Many other substances with possible benefits in the treatment of xerosis are under study. Glycerol, in particular, seems to play an important role in stimulating the expression of epidermal aquaporin-3. The better function of these aquaporins results in improvement of skin barrier

function and skin hydration [53, 54]. Antipruritic agents, such as glycine, which can block histamine release from mastocytes, seem to be useful in breaking the itch–scratch cycle. Finally, some topical formulations include an active ingredient that stimulates cell proliferation and lipid synthesis: dexpanthenol is an example of this class of ingredient [54, 55].

Various emollient formulations, including lotions, creams, and ointments, are available, and attention to patient need is important to secure compliance. The choice of the emollient should be ideally discussed with the patient, and may be driven by cosmetic acceptability, cost, oil content, and adjuvant properties such as humectant and/or anti-itching properties. Patients may require different types of emollient product, depending of the area of the body to be treated, the patient's lifestyle, and seasonal factors.

The benefits of emollient use on health economics are many: they help to control flares of AD, reduce referrals, and improve the quality of life of patients. To obtain these objectives emollient products should remain on prescription, and prescribers should be aware of the costs and properties of the various emollients. Humectant-containing products can produce greater barrier repair per gram than an emollient without humectants [5].

Emollients should be applied correctly and generously; sufficient quantities must therefore be prescribed, and patient education is crucial for maximum effect of therapy. They should be routinely applied by being gently rubbed into the skin after a bath or shower because there is some evidence that this will help trap moisture in the skin. Ideally, emollients should be applied several times a day to keep the skin hydrated.

If inflammation becomes severe, topical corticosteroids may be needed for short-term use. Emollients should be continued while the patient is on corticosteroid therapy.

Adverse Effects of Topical Treatment for Xerosis

Serious reactions are rare, and the most common adverse effects of topical treatment are irritant and allergic contact dermatitis. Irritant contact dermatitis is more common and is caused by frequent and prolonged use of preparations containing potential irritants such as sodium lauryl sulfate. Contact allergic dermatitis is a delayed hypersensitivity reaction to an allergen whereby the initial sensitization exposure must occur first in order to activate immune system response. It is important, therefore, to avoid skin sensitizers such as wound-care agents in patients with xerosis, in whom the cutaneous barrier is impaired. Table 66.4 lists common skin sensitizers found in emollients that should be avoided, if possible.

Humectants such as urea and lactic acid are associated with a subjective sensation of mild burning in some individuals, but are generally tolerable [56, 57].

Table 66.4 Common skin sensitizers that may be found in emollients

Balsam of Peru
Lanolin
Propylene glycol
Parabens
Formaldehyde
Fragrance
Vitamin E
Aloe vera
Methylchloroisothiazolinone/methylisothiazolinone (Kathon CG)

Future Perspectives

The growing knowledge of the mechanisms involved in the xerosis process makes it increasingly possible to choose the most appropriate emollient for an individual patient based on specific epidermal disarrangement.

Considering the great number of emollients available today, it is of absolute importance to develop studies that compare different active substances. Only through such studies will the choice of treatment be based on better efficacy.

Finally, because the recent advances in our understanding of the pathogenesis of xerosis, the development of new classes of compounds will be an imminent reality in the next few years.

Glossary

Ceramide The basic unit of the sphingolipids, consisting of sphingosine (unsaturated amino alcohol) or a related base attached via its amino group to a long-chain fatty acid anion. A lipid molecule that plays a fundamental role in skin water.

Emollients Complex mixtures of chemical agents specially designed to make the external layers of the skin (epidermis) softer and more pliable. They increase the skin's hydration (water content) by reducing evaporation. Emollients work by forming an oily layer on the top of the skin that traps water in the skin.

Humectants Substances that absorb water from the atmosphere and also from the lower layers of the skin, making more moisturized the upper skin that is palpable.

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Hyperhidrosis

67

Doris Hexsel and Fernanda Oliveira Camozzato

Key Points

- Sweating is a normal and important mechanism of thermoregulation which is essential for survival. When excessive, it is called hyperhidrosis.
- It is necessary to understand the biology of eccrine, apocrine, and apoeccrine sweat glands to understand hyperhidrosis.
- Hyperhidrosis can be primary (idiopathic/essential) or secondary to another condition. Hyperhidrosis can be further classified as focal or generalized.
- Primary hyperhidrosis is most often focal, affecting the palms, soles, and axillae. Thighs and gluteal and inguinal regions may also be involved. One or more regions can be affected in the same patient.

- Secondary hyperhidrosis must be ruled out before a diagnosis of primary hyperhidrosis is made. A variety of conditions can induce hyperhidrosis.
- There are many treatments for hyperhidrosis, including aluminum compounds, iontophoresis, botulinum toxin, drugs, microfocused ultrasound, and endoscopic thoracic sympathectomy.

Introduction

Hyperhidrosis is a chronic autonomic disorder whereby the production of sweat exceeds the amount required for thermoregulation. This condition is not merely characterized by excessive sweating but also by any amount of sweating that causes physical, emotional, and social discomfort for the patient [1]. Hyperhidrosis may impair the ability to perform daily functions and, in some cases, may increase the risk of cutaneous infections because of the continuous dampness of the skin [2]. Patients with hyperhidrosis have a decreased quality of life, which is comparable with that observed in patients with acne vulgaris or psoriasis [3, 4].

Hyperhidrosis can be classified as a primary or secondary disorder, and may have focal or generalized manifestations [5]. Primary hyperhidrosis

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is most often focal and usually causes idiopathic, symmetrically bilateral excessive sweating [6]. Secondary hyperhidrosis manifests most often as generalized excessive sweating related to an underlying medical condition or to the use of a medication [5]. The cause of hyperhidrosis should always be investigated and treated whenever possible.

Epidemiology

Currently hyperhidrosis affects about 1–3% of the population [7, 8]. One epidemiologic survey estimated that 0.5% of the US population may be suffering from the effects of hyperhidrosis, with major interference in daily activities [6]. However, this number may be underestimated, because hyperhidrosis is underreported by patients and underdiagnosed by healthcare professionals [6]. A study conducted in the United States to determine the prevalence of hyperhidrosis sent a survey inquiring about excessive sweating to 150,000 US households and concluded that 2.8% of the US population is affected by hyperhidrosis [6].

Data suggest no difference in the incidence between men and women [6]. However, studies in Japan [7] and Germany [8] found that the incidence of hyperhidrosis is higher in men than in women: 16.66% versus 10.66% and 18.1% versus 13.3%, respectively. Men reported higher intensity of hyperhidrosis symptoms than women in a study of Polish students [9], but in a study of Canadian patients, women reported being more severely affected than men [10]. Another study found that the most patients with hyperhidrosis (93%) had primary hyperhidrosis [5].

The onset of primary hyperhidrosis usually takes place between the ages of 14 and 25 years. When the onset happens at a prepubertal age, normally the palmar or plantar areas are affected, with presentations in the axillary, facial, or abdominal and dorsal regions less likely. A postpubertal onset is more often associated with an axillary distribution [10].

A positive family history is present in 35–56% of patients with hyperhidrosis. The inheritance pattern has a variable penetrance and is most likely autosomal dominant [2, 6, 10]. However, one study found a higher association with a positive family history in patients with primary palmar hyperhidrosis, with 65% of patients having a positive family history [11]. Earlier age at onset (<20 years of age) also correlated with a positive family history [10].

Hyperhidrosis is potentially underdiagnosed and undertreated. To properly diagnose this condition the physician should question the patients, during a routine review of systems, about sweating and how it affects the patient's quality of life.

Etiopathogenesis

The skin appendages are composed of the eccrine and apocrine sweat glands, the hair follicles, the sebaceous glands, and the nails. All of these are embryonically derived from buds of epidermis that grow down into the dermis to form these specialized structures.

Eccrine sweat glands are distributed all over the body surface, except in the external auditory conduit, vermilion border, nail bed, clitoris, and labia minora [12]. These glands are most numerous on the palms, soles, face, axilla, and, to a lesser extent, the back and chest [13]. The number varies greatly with site, occurring more densely on the soles compared with the thighs, and also vary in size from person to person [12]. Histologically, the eccrine gland is divided into three subunits with a snarled secretory portion located at the dermal–hypodermal junction or lower dermis; in an intradermal sweat conduit, which also constitutes half of the basal layer; and in an intraepidermal sweat conduit [14]. The secretory portion consists of an external layer of contractile myoepithelial cells that mobilize sweating secretion. These cells secrete a hypotonic saline solution and are innervated by cholinergic postganglionic sympathetic nerve fibers [15, 16] responding to the cholinergic stimuli. There is no relationship between the density of eccrine glands in normal individuals and the density of eccrine glands in those who suffer from focal hyperhidrosis [17].

Apocrine sweat glands (ASG) are part of the pilosebaceous unit [15] that is composed of hair follicles and sebaceous glands. Apocrine glands are specialized sweat glands that secrete a solution with high oil content and are under adrenergic control [18]. Apocrine glands are usually restricted to a few regions such as axillae, anogenital region, periumbilical region, perimammary area, prepuce, scrotum, in a modified form of glands in the external auditory conduit (ceruminous glands), eyelids (Moll glands), and mamma (mammary glands) [18, 19]. In the normal axillary region, apocrine glands outnumber eccrine glands by approximately 10 to 1 [13]. Histologically, ASG may be divided in three segments: a secretory portion, an intradermal channel, and an intraepidermal channel [17]. The secretory portion is composed of a single layer of columnar cells whose size reflects their secreting activity [18]. These glands release a portion of their cytoplasm into the glandular lumen, which is called decapitation secretion [18]. Proteins, ammonia, sugars, fatty acids, and sometimes chromogens constitute the apocrine secretion. The secretion is odorous, and it is assumed that the odor is due to products excreted by local bacterial skin flora [19]. The function of apocrine glands in humans is not fully elucidated, although it is thought that they may be important for body odor and pheromones [17]. They are activated after reaching sexual maturity.

A third type of gland, described by Sato et al., was termed "*apoeccrine*" because they contain morphologic features common to the other two types [20]. Histologically this gland is subdivided into three portions, with a secretory portion, which features an irregular dilated segment and another nondilated segment; an intradermal channel; and an intraepidermal channel. Secreting cells resemble the eccrine gland light cells in the nondilated segment; however, they resemble apocrine glands in the dilated region [20]. Ductal opening occurs at the epidermal level, as is the case for eccrine glands [21]. Apoeccrine glands receive sympathetic innervation and respond to cholinergic stimuli and epinephrine. They apparently develop after adolescence in both sexes [20]. These glands produce copious, watery fluid and can represent 10–45% of all axillary glands [19].

The degree to which each gland type is involved in hyperhidrosis is unknown, but is believed to be of eccrine origin because of its profuse nature and watery consistency [17, 21]. This fact, however, does not exclude the possibility that other glands may be involved [17, 21].

The cause of hyperhidrosis is unknown, but it has been postulated that this condition occurs as a primary process of autonomic neuronal dysfunction, as the sweat glands and their innervation do not show any histologic abnormalities. This dysfunction tends to occur in areas where there is a higher concentration of eccrine glands such as the palms, soles, and axillae, which are sweat-producing glands. Less common sites are the scalp or face [15].

A central sudomotor efferent pathway is suggested for hyperhidrosis with the following connections: (1) cerebral cortex to hypothalamus; (2) hypothalamus to medulla; (3) fibers crossing in the medulla oblongata and travelling to the lateral horn of the spinal cord; (4) the lateral horn to sympathetic ganglia; and (5) sympathetic ganglia to sweat glands as postganglionic C fibers [15]. Sweat gland innervation is sympathetic and postganglionic, with acetylcholine as primary neurotransmitter [18]. These fibers consist of unmyelinated class C fibers [15]. Norepinephrine and vasoactive intestinal peptide (VIP) may play a role, but neither of these amplifies cholinergic sweat secretion [22].

Emotional stimuli alone can activate sweat glands. Frontal and premotor projections to the hypothalamus probably promote sweating during enhanced emotions [18]. The hypothalamic sweat center, which is in charge of the palms, soles, and in some individuals the axilla, seems to be distinct from the other hypothalamic sweat centers and is actually under exclusive control of the cortex, with no input from the thermosensitive elements. Because emotional sweating does not occur during sleep or sedation, one of the criteria for primary hyperhidrosis is that the individual does not experience sweating during sleep. Sympathetic cholinergic nerves activate both thermoregulatory and emotional sweating and are controlled by different central nervous system neurons. It is possible that primary hyperhidrosis is due to abnormal

central control of emotional sweating, given that it affects the same body areas as those affected in emotional sweating (hands, feet, and axillae) [23].

Classification

Primary Hyperhidrosis

Primary hyperhidrosis is excessive sweating in specific regions of the body, the sweating itself being the medical problem [5]. *Primary hyperhidrosis* is usually symmetric, starts in childhood or in the second decade of life, and is often hereditary. This form of hyperhidrosis is not secondary to medical conditions or medications, and the diagnostic criteria are shown in Table 67.1.

Table 67.1 Criteria for diagnosis of Hyperhidrosis [5, 54, 67]

Primary hyperhidrosis	Excessive sweating focal and visible of at least 6 months' duration without any apparent cause and at least two of the following:
	Bilateral and relatively symmetric
	Impairs daily activities
	At least one episode per week
	Age of onset <25 years
	Family history of hyperhidrosis
	Cessation of focal sweating during sleep
	Exclusion of secondary causes of excessive sweating
Secondary generalized hyperhidrosis	Generalized excessive sweating attributable to a definitive underlying medical cause: most commonly drugs, cardiovascular disorders, respiratory failure, infections, malignancies, endocrine disease, metabolic disorders, neurologic disease, among others
Secondary focal hyperhidrosis	Excessive sweating in typical anatomic sites as palms, soles, axillae, craniofacial, or in a well-defined anatomic distribution such as trunk, inguinal folds, buttocks, legs, submammary folds, neck, or wrist *and* identification of a definitive underlying cause; most commonly Frey syndrome, eccrine nevus, social anxiety disorder, neurologic disorder, or tumor

Adapted from Walling [5]

When excessive sweating affects only a specific part of the body it is called localized hyperhidrosis [1]. Common focal sites for primary hyperhidrosis include palms, soles, axillae, craniofacial area, inguinal area, and gluteal region. Palmar, plantar, and axillary hyperhidrosis are the most common [5, 6]. Patients with primary hyperhidrosis may have one or multiple sites of involvement, as palmar hyperhidrosis alone, palmar and axillary hyperhidrosis, or various other combinations of focal involvement [6, 24].

Axillary Hyperhidrosis

Axillary hyperhidrosis (AH) is excessive sweating specifically in the area of the axillae and usually presents with a bilateral pattern. While it can be continuous, it is more commonly phasic. It may be precipitated by heat, mental stress, or exercises [25] and is associated with dermatologic complications including pompholyx, contact dermatitis, bromhidrosis, chromhidrosis, and intertrigo [26]. Its onset is usually after puberty.

Plantar and Palmar Hyperhidrosis

In palmoplantar hyperhidrosis the feet and hands are often cold because of perspiration evaporation, which also stimulates the sympathetic nervous system and contributes to aggravating hyperhidrosis [27]. This form of hyperhidrosis constitutes a substrate for the establishment of fungal infection and contact dermatitis. It fosters the appearance of bacterial infections and keratolysis plantare sulcatum, whereas palmar hyperhidrosis may be associated with dyshidrosis.

Inguinal Hyperhidrosis or Hexsel's Hyperhidrosis

Hexsel's hyperhidrosis is often associated with other forms of hyperhidrosis [28]. It symmetrically affects the groin region, including the suprapubic area, the shallow depression that lies immediately below the fold of the groin, the medial surfaces of the upper inner thighs, and the genital area. It may also include the lower part of the gluteus maximus, gluteal fold, and natal cleft [29]. Patients with this condition have difficulty in concealing the often-embarrassing sweat-drenched clothing in this area that typically results from having the disorder.

Prevalence is largely unknown because of under-reporting, but the condition appears less frequently than other forms of focal hyperhidrosis. Fifty percent of patients with Hexsel's hyperhidrosis have a positive family history of some form of hyperhidrosis, suggesting an inherited mechanism [29].

Localized Unilateral Hyperhidrosis

Localized unilateral hyperhidrosis is usually seen as a sharply demarcated region of sweating on the forearm or forehead restricted to less than 10 × 10 cm. Most cases are idiopathic with no triggering factors. The pathogenesis is unclear [30], and one case report suggests that there is a hypohidrotic element to the disorder [31]. Fewer than 40 cases have been reported in the literature [31].

Secondary Hyperhidrosis

Secondary hyperhidrosis is usually generalized and is due to an underlying cause. This condition can be further classified as focal or generalized.

Secondary Generalized Hyperhidrosis

Secondary generalized hyperhidrosis is caused by a medication or a medical condition. Conditions that may cause secondary hyperhidrosis can be physiologic, such as pregnancy, menopause, fever, excessive heat; or pathologic, including malignancy, lymphoma, carcinoid syndrome, diabetes mellitus, thyrotoxicosis, diabetes insipidus, hyperthyroidism, pheochromocytoma, tuberculosis, HIV (human immunodeficiency virus), endocarditis, and autonomic dysreflexia, among others [5, 32, 33]. There are many drugs that are known to cause secondary hyperhidrosis, including antidepressants, hypoglycemic agents, tryptans, antipyretics, cholinergics, sympathomimetic agents, and many others. Psychiatric disorders can also present with hyperhidrosis. Secondary hyperhidrosis is a clinical feature in 32% of persons with social anxiety disorder [34, 35]. Some debate exists, however, over whether the relationship between these two entities is causal [36].

Secondary causes of hyperhidrosis must be ruled out before diagnosing primary hyperhidrosis [5, 32]. This is best accomplished by a complete review of systems and additional follow-up as appropriate based on the patient response. Some clinical features help distinguish between primary and secondary types of hyperhidrosis and include onset of the disease, characteristics of the sweating, and associated symptoms [5]. The onset of symptoms in patients with secondary hyperhidrosis is more likely later than in patients with primary hyperhidrosis. Patients with secondary hyperhidrosis are more likely to exhibit unilateral or asymmetric sweating, or be generalized, and to have symptoms during sleep ("night sweats"). Secondary hyperhidrosis is less often associated with positive family history [5].

Secondary Focal Hyperhidrosis

Although rare, multiple types of focal secondary hyperhidrosis exist.

Gustatory Sweating

Gustatory sweating is characterized by profuse sweating of the face, scalp, and neck [37]. A physiologic type of gustatory sweating occurs as bilateral facial sweating secondary to heat or to the ingestion of hot or spicy foods. Nonphysiologic types of gustatory sweating are caused by sympathetic nerve damage from neoplasm or sympathectomy, auriculotemporal nerve syndrome, diabetic neuropathy, or infection [37–39].

Gustatory sweating is a common postsurgical complaint occurring in patients after parotidectomy, usually for adenoma. It can be a component of Frey's syndrome, which also includes parotid flushing. Frey's syndrome may occur in up to 60% of patients after parotidectomy with facial nerve dissection [39]. Auriculotemporal nerve syndrome can occur sporadically as a familial trait or be due to a preceding trauma to the nerve. Diabetic gustatory sweating may occur as a by-product of sympathetic denervation, which is compensated by innervation of aberrant parasympathetic fibers [38]. These fibers stem from the minor petrous nerve and innervate the

parotid gland, causing sweating when salivation is induced. This finding is seen in 69% of patients with diabetic nephropathy and 36% of patients with diabetic neuropathy [37]. Gustatory sweating may also occur after infection, most commonly secondary to herpes zoster infection [33].

Cutaneous Disorders

Secondary focal hyperhidrosis may be seen in conjunction with a variety of cutaneous disorders, although a causal relationship has not been established. Disorders include eccrine nevus, pachyonychia congenita, palmoplantar keratodermas, glomus tumor, blue rubber bleb nevus syndrome, nevus sudoriferous, POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes) syndrome, speckled lentiginous nevus syndrome, Riley–Day syndrome, pachydermoperiostosis, Gopalan syndrome, pretibial myxedema, Buerger disease, eccrine pilar angiomatous hamartoma, local injury, and increased size of eccrine glands [40, 41].

Eccrine nevus or nevus sudoriferous can cause localized hyperhidrosis in an area of skin with increased numbers of eccrine glands [42]. Associated hypertrichosis and comedones can be seen in the area. A similar lesion, eccrine angiomatous hamartoma [43], shows an abundance of eccrine glands and a proliferation of vascular channels. Because of clinical and histologic similarities, these lesions may share a similar genetic pathway.

Pachyonychia congenita is a rare autosomal dominant genodermatosis that is often associated with focal palmar and plantar hyperhidrosis. One study found hyperhidrosis in 51.5% of all patients with pachyonychia congenita and in 22.7% of children with the disorder [44].

Other Forms of Secondary Hyperhidrosis

Some types of secondary hyperhidrosis are characterized by anhidrosis in one area with compensatory hyperhidrosis in another area. Most commonly the condition is iatrogenic, in the form of compensatory sweating following surgical treatment of primary focal hyperhidrosis. It may also manifest as part of Ross syndrome or in one of several neurologic conditions [45, 46].

Compensatory hyperhidrosis is a known potential complication of endoscopic thoracic sympathectomy (ETS), which occurs in areas that do not present abnormal preoperative sweating. Its intensity varies [47] and can worsen with climate changes and heat, as well as with psychological and emotional alterations. It can affect the inferior portion of the chest (generally below the nipple), dorsal and lumbar region, abdomen, pelvic waist, popliteal fossa, and lower limbs. An expert consensus of the Society of Thoracic Surgeons reported that 3–98% of patients having had ETS develop iatrogenic compensatory hyperhidrosis [48]. One large-scale study found that only 55% of patients developed compensatory sweating [49].

Ross syndrome is a rare nervous system disorder, with about 50 case reports in the literature [50] characterized by a tonic pupil ("Adie pupil"), deep tendon hyporeflexia, and unilateral or bilateral anhidrosis [46]. It can present with associated segmental hyperhidrosis. Recent studies suggest that Ross syndrome may have autoimmune etiology [45].

Secondary regional hyperhidrosis may be related to stroke, spinal cord lesion, neoplasm, or peripheral neuropathies [51, 52]. One pathophysiologic explanation for this phenomenon is that the primary lesion causes impairment of preganglionic neurons and subsequent anhidrosis, but bladder distension and other visceral stimuli enter the spinal cord distal to the lesion, causing a spinal dysreflexia that manifests as abnormal sweating. The phenomenon has also been called "perilesionary hyperhidrosis" or "border-zone sweating" [51]. Hyperhidrosis can also be associated with syringomyelia and other central nervous system diseases [53].

Associated Factors and Conditions

Heat, stress levels, and physical activities can aggravate hyperhidrosis. Other possible aggravating factors are sexual activity, excessive intake of liquids, weight increase, premenstrual tension, prolonged sitting, and wearing synthetic clothing. Cold acts as an attenuating factor. Some patients also refer to the absence of stress as an attenuating factor.

Hyperhidrosis can also be a triggering and a sustaining factor of other diseases in the affected

sites. Besides the excessive sweating, these associated diseases can be aggravated by contact with clothing or products used in the area to decrease perspiration [11], or by the increase in local moisture, with consequent skin maceration and proliferation of microorganisms. The most frequent associated diseases are bacterial and fungal infections, but pompholyx, contact dermatitis [26], folliculitis, erythrasma, and dermatitis can occur. Patients suffering from hyperhidrosis frequently mention bromhidrosis, chromhidrosis, and skin color changes in the inguinal region.

Diagnosis

The criteria for diagnosis of hyperhidrosis are summarized in Table 67.1 [5, 54]. Patient history usually provides all the information required to differentiate common primary hyperhidrosis from potentially worrisome causes (Fig. 67.1) [55].

Asymmetric hyperhidrosis should prompt an investigation for a neurologic lesion. Generalized primary hyperhidrosis is rare, and the diagnosis is made after causes of secondary sweating are excluded.

Some tools are useful for the diagnosis and assessment of hyperhidrosis severity. The Minor test is an important instrument to localize the hyperactive sweat glands in different forms of hyperhidrosis and to assess the response to treatment. This test does not quantify the severity of hyperhidrosis [56], but identifies different sweating intensities. Hexsel and coworkers proposed the Sweating Intensity Visual Scale to classify the sweating intensity. This is a visual 6-grade scale based on the final color resulting from the Minor test: Grade 0 = minimal or no sweating; Grade I = initial, discrete sweating; Grade II = mild sweating; Grade III = moderate sweating; Grade IV = intense sweating; and Grade V= excess sweating [57]. There are also other tools for the assessment of
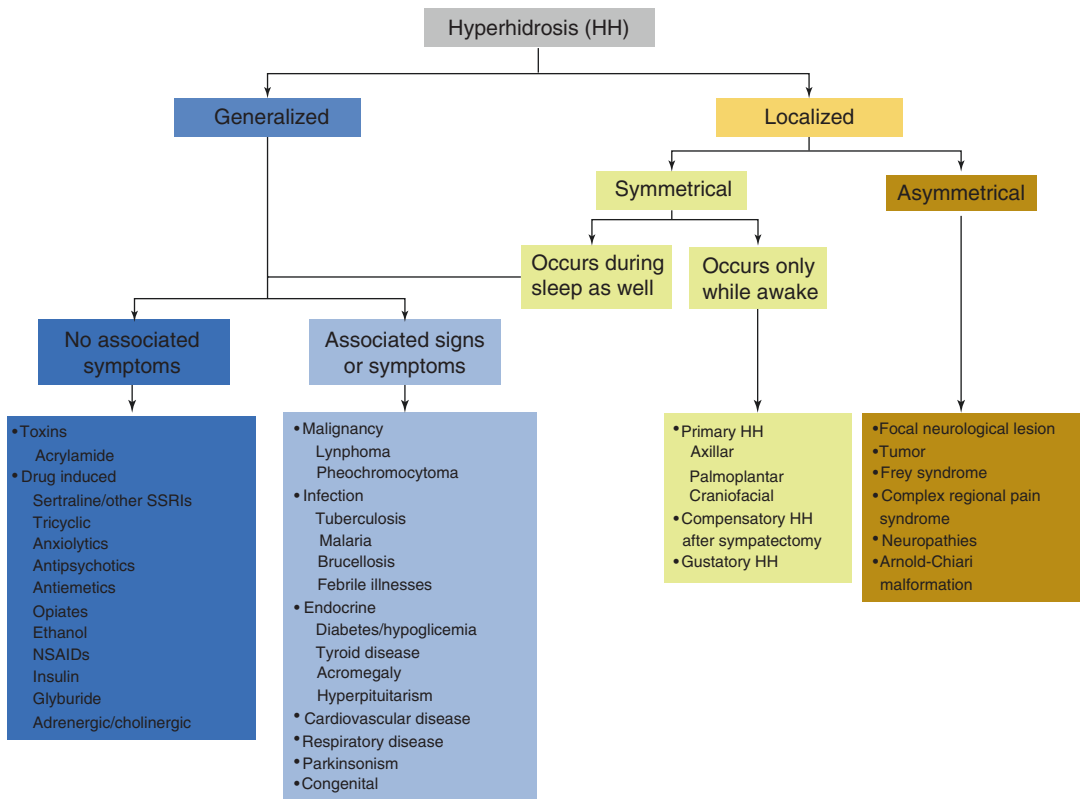
Fig. 67.1 Diagnostic algorithm for evaluation of the patient with pruritus (Adapted from Vary [55])

hyperhidrosis severity, such as the 4-point single-question Hyperhidrosis Disease Severity Scale [56], gravimetry, [58] and the Hyperhidrosis Area and Severity Index [59].

Therapeutic Approach

Depending on the type, location, and severity of the hyperhidrosis, different treatments can be used, including topical, oral, and iontophoretic treatments, botulinum neurotoxin (BoNT) injections, and surgery. To date, an established level of evidence (level A, two or more class I papers) [60] exists only for BoNT-A treatment of axillary hyperhidrosis. Some nonpharmacologic treatments can control the disease.

The Canadian Hyperhidrosis Advisory Committee designed an algorithm to guide the treatment of hyperhidrosis [56]. Mild axillary, palmar, and plantar hyperhidrosis should firstly be treated with topical aluminum chloride. In case of failure, BoNT-A or iontophoresis should be considered. In severe cases, BoNT-A and topical aluminum chloride are first-line therapy. For palmar and plantar hyperhidrosis, iontophoresis is also first-line therapy. First-line therapies for craniofacial hyperhidrosis, regardless of disease severity, include oral medications, BoNT-A, or topical aluminum chloride. Local surgery and endoscopic thoracic sympathectomy should be considered in severe cases of hyperhidrosis, mainly when the patient fails to respond to all other treatment options [56].

Nonpharmacologic Treatment

Weight control In general, an increase in body mass index is associated with an increased need to sweat. Therefore, keeping body mass index within the normal range helps patients with hyperhidrosis [47].

Nonthermogenic diet Some foods activate the sympathetic nervous system, leading to metabolic and endocrine responses after their intake. Such foods include certain legumes, pepper, garlic, coriander, cin-

namon, ketchup, salt, ginger, chocolate, coffee, pork, viscera, red meat, milk, milk derivatives, strawberries, cola-based soft drinks, and mate (*Ilex paraguariensis*) infusion, as well as black, green, and chamomile tea [47]. Regarding the diet composition, proteins are the highest contributors to activating the sympathetic nervous system (i.e., they activate thermogenesis), followed by carbohydrates. The intake of food supplements with high quantities of proteins and carbohydrates can also trigger increased sweating.

Physical exercise A daily 30-min walk can help avoid weight increase in sedentary individuals, and additional exertion is sufficient to lose weight and reduce the body mass index.

Clothing Clothes, either social or professional, have to be tolerable to the patient. A thin dry-fit T-shirt or cotton shirt can help distribute the sweat more evenly when used under the clothes [47]. Changing clothes one or more times a day is often necessary, especially on hot, humid days.

Weather conditions Ambient temperature plays an important role in cooling the human body. The thermal sensation of heat increases when the environment is hotter, more humid, and less ventilated, with a consequent increase in sweating intensity. The patients present improvement of the symptoms in cold environments with low humidity and good ventilation [47].

Topical Treatments

Aluminum salts are the main topical agents for hyperhidrosis. Their mechanism of action is attributed either to an interaction between aluminum chloride and keratin in the sweat ducts or to a direct action on the excretory eccrine gland epithelium [61]. Solutions of aluminum chloride concentrations vary between 12% and 20% formulations. Higher concentrations of aluminum chloride and higher salt content in preparations commonly cause irritation or burning, which can limit use. The sweat glands of primary hyperhidrosis are less active during sleep, allowing the metal salts to remain in place when applied at night [62]. Topical agents can be used

in all forms of hyperhidrosis (axillary, palmoplantar, and gustatory), although these are more commonly used for axillary and palmar hyperhidrosis. These solutions are effective in milder [62] and severe cases [56] of hyperhidrosis as the duration of effect is often limited to 48 h.

Newer topical preparations have shown an improvement in tolerability, such as a combination of 15% aluminum chloride with 2% salicylic acid gel [63]. The addition of salicylic acid may improve tolerability by hydrating and mitigating the drying effect of alcohol, and may also act synergistically with aluminum chloride given its astringent and antiperspirant properties. Tolerability may also be improved with use of a 20% aluminum chloride spray in a silicone base [63].

Topical anticholinergic preparations such as topical glycopyrrolate improved sweating in certain patients, but efficacy is not consistent [64, 65]. Furthermore, some evidence suggest that the effect may involve systemic absorption of the anticholinergic medication [66–68].

Oral Treatments

Oral treatments can offer significant benefit, but the doses required for clinically meaningful effect cause significant and undesired side effects. Anticholinergic agents (glycopyrrolate, menthatheline bromide, oxybutynin, atropine, and scopolamine) and α-adrenergic agonists (clonidine) are the most used in clinical practice. Anticholinergic agents work by inhibiting the production of acetylcholine at muscarinic receptors [69].

Oxybutynin chloride is a promising medication. This drug can be of great help in the control of primary hyperhidrosis or in compensatory hyperhidrosis when patients tolerate its side effects. The use of oxybutynin has been reported as a therapeutic option in children with hyperhidrosis [70, 71]. It is effective for 6–10 h, or even up to 24 h if continuous-use formulations are taken. The lowest dose of oxybutynin is 5 mg at bedtime, at which dosage patients are not likely to present side effects. Generally the effective dosage requires the intake of 15 mg a day: three intakes of 5 mg fractionated over the course of the day.

A retrospective study [72] included 110 patients with hyperhidrosis treated with oxybutynin. After 3 months of treatment, 79% responded. After 12 months, 62% continued to respond, and the response was considered excellent in 50%. Most of the patients who responded at 3 and 12 months reported mild adverse events. No serious adverse events were observed. Uptitrating the dosing regimen resulted in higher treatment adherence rates than a fixed-dose regimen.

In some cases, the side effects of anticholinergic drugs result in noncompliance with treatment, leading many patients to use these drugs only on social occasions and at the lowest necessary dose. Side effects can be very disabling and include dry mouth, blurring of vision, urinary hesitancy, dizziness, tachycardia, and confusion [69]. Contraindications include myasthenia gravis, pyloric stenosis, narrow-angle glaucoma, and paralytic ileus. Gastroesophageal reflux disease, glaucoma, bladder outflow obstruction, and cardiac insufficiency are relative contraindications.

Oral agents can be used in all subtypes of hyperhidrosis such as axillary, palmoplantar, craniofacial/gustatory, and generalized. However, double-blind studies are available only for axillary and palmoplantar hyperhidrosis. Current evidence indicates that both oxybutinin (one class I study and one class II study) and menthatheline bromide (two class II studies) are probably effective, with level B evidence. Retrospective studies suggested oral glycopyrrolate and clonidine are also effective. Collectively, oral agents have level B evidence (probably effective) with one class I study and three class II studies present in the literature [73].

Iontophoresis

Iontophoresis is the introduction of an ionized substance through application of a direct current on intact skin [74]. Although the exact mechanism of action is unknown, this technique facilitates transdermal movement of solute ions by generation of an electrical potential gradient. This process decreases the perspiration production in the treated areas, partially improving the symptoms [75, 76]. Repeated treatments are

required [76]. Although there are devices with special configurations to treat the axilla, palm, and sole regions, there is no special configuration for the inguinal region. Devices for home use are very cost-effective after the initial investment. Tap water over the metal plates improves contact with the skin and provides a source of ions. Iontophoresis is performed initially every 2–7 days, until a therapeutic effect is achieved, after which the treatment can be performed once every 2–3 weeks [74]. Implantable electronic devices such as pacemakers or defibrillators, artificial joints, and application in pregnant women are contraindications.

Botulinum Neurotoxin Type A (BoNT-A) Treatment

BoNT-A is one of the most effective therapies for localized hyperhidrosis. BoNT-A is an inhibitor of acetylcholine release from the presynaptic membranes of neuromuscular junctions, thus preventing cholinergic transmission to postganglionic neuroreceptors. The treatment is applied in focal sites of localized hyperhidrosis such as axilla, palms, soles, face, and scalp. Compensatory hyperhidrosis can be also treated with BoNT-A [47]. Side effects include pain and possible transitory muscle weakness.

As a painful procedure, anesthetic creams and local or truncal anesthesia are useful to increase patient comfort. Trichotomy of the region may be necessary. Minor's test performed in the hyperhidrosis zone delimits the area. Bearing in mind that the sweat glands are located about 2.5 mm below the skin [77], the application should be intradermic, preferably using fine-gauge needles, such as 30-gauge. A simple technique to avoid overly deep injections is to use a cut needle lid over the needle as a shield [78]. Minor's test can be repeated about 1 month after the procedure to identify any residual perspiring areas.

The field of anhidrotic effects of BoNT-A does not vary significantly when the same doses in different dilutions and depths are injected on the back of patients suffering from compensatory hyperhidrosis [79]. However, areas of more intense sweating such as midline demand higher doses to achieve a similar field of anhidrotic effects [79]. These results support that dose is more important than brand, usual dilutions, and depths in determining the size or area of the field of anhidrotic effects [79]. Ideal doses have been the focus of discussion, aiming to obtain more efficacious and lasting results Table 67.2 lists some articles and the proposed doses for the treatment of axillary, inguinal, and palmar hyperhidrosis and the average duration of effects.

Lasers and Microwave-Based Treatment

The efficacy of laser treatments for hyperhidrosis remains unclear. A pilot study evaluated a long-pulsed neodynium yttrium aluminum garnet (1,064 nm Nd:YAG) laser and showed improvement of sweating in patients with axillary hyperhidrosis for up to 9 months compared with the control group [89]. However, another study of Nd-YAG laser hair removal therapy showed a side effect of hyperhidrosis in the treated areas [90].

Microwave energy is a new technology and a nonsurgical option for hyperhidrosis treatment [91–93]. It targets the skin and subcutaneous tissue interface, which causes irreversible thermolysis of eccrine glands. Nestor and Park [94] reported the results of two randomized double-blind, sham-controlled pilot studies with the Ulthera® system (Ulthera, Mesa, AZ, USA) to treat patients with axillary hyperhidrosis. The results showed significant and long-lasting reductions in baseline sweat production, high levels of patient satisfaction, and only minor transient discomfort during treatment [94].

Surgical Therapy

Surgical approaches for focal hyperhidrosis include excision of sweating areas, curettage, liposuction, and thoracic sympathectomy [48]. These procedures are typically reserved for patients who have failed conservative therapy or are not candidates for previously described therapies [56].

Table 67.2 Proposed dose regimens for the treatment of axillary, inguinal, and palmar hyperhidrosis

Authors	HH area	Study design	Patients	Treatment	Results	Duration
Heckmann [80]	Axillary	R, DB, PC, multicenter	158	200 U (ABO) unilaterally vs placebo. Placebo-treated side received 100 U (ABO) after 2 weeks	Equal reductions in sweating with the two doses	26 weeks for both groups
Naumann and Lowe [81]	Axillary	R, DB, PC, parallel group	320	50 U (ONA) vs placebo	Response at week 4: 94% (active group) vs 36% (placebo). At week 16: 82% (active) vs 21% (placebo),	16 weeks
Saadia et al. [23]	Palmar	R, SB comparison of 2 doses, intraindividual	24	50 U (ONA) vs 100 U (ONA) in each palm	At 1 month: significant decrease in sweating. At 6 months: anhidrotic effect evident in both dose groups	6 months
Odderson [82]	Axillary	R, DB, PC	18	100 U (ONA) vs placebo	At 2 weeks: sweat production decreased 91.6% in BoNT ($p < 0.05$). At 5 months: 88.2% reduction in BoNT	5 months
Simonetta Moreau et al. [83]	Palmar	R, DB, active comparator, intra-individual comparison	8	69 U (ONA) or 284 U (ABO) (mean dose)	At 1 month: decrease in mean palmar sweating area: 76.8%, ABO vs 56.6% ONA At 3 months: decrease in sweating area was 69.4%, ABO and 48.8%, ONA	17 weeks ABO 18 weeks ONA
Hexsel [29]	Inguinal	Case series	26	100 U (ONA) 60 and 80 U (ONA) can be used to treat less severe cases	Improvement showed for inguinal HH for first time	6–8 months
Lowe [84]	Axillary	R, DB, PC, multicenter, parallel-group	322	50 or 75 U (ONA) or placebo	At 4 weeks: 75% of subjects in active groups vs 25% from placebo	197 days in the 75-U group and 205 days in 50-U group
Vadoud-Seyedi and Simonart [85]	Axillary	R, DB, side by side	29	100 U (ONA) total dose in both axillae, reconstituted in saline or lidocaine	Similar time of onset and duration of effect, and decrease in sweating. Significantly lower pain in axillae treated with lidocaine-BoNT (29.3 vs 47.5)	8 months

(continued)

Table 67.2 (continued)

Authors	HH area	Study design	Patients	Treatment	Results	Duration
Talarico [86]	Axillary	DB, R, prospective	10	50 U (ONA) in one axilla and 150 U (ABO) in the other	Sweat rate decreased 97.7% in ONA axilla and 99.4% in ABO axilla	260 days for ONA and 290 days for ABO
Gregoriou [87]	Palmar and plantar	Open label	36	100 U (ONA) per palm	Significant improvement in palmar HH	6.2 months
Dressler and Adib Saberi [88]	Axillary	DB, intra-individual comparison	51	First: 100 U (ONA) bilaterally; then: direct comparison 100 U (ONA) unilaterally vs 50 U (ONA) contralaterally	Both doses had similar effects	3–4 months

ABO abotulinumtoxin A, *BoNT* botulinum neurotoxin, *DB* double-blind, *HH* hyperhidrosis, *ONA* onabotulinumtoxin A, *PC* placebo-controlled, *R* retrospective, *SB* single-blind

Curettage or liposuction cannula and surgical excision of glands are mainly indicated for axillary hyperhidrosis. Insertion of a liposuction cannula or curette via a small incision allows near-complete removal of the glands. Local hematoma, seroma, or necrosis can occur, as well as recurrence [95]. In other focal forms, these procedures may result in unacceptable scars.

ETS is mostly indicated for palmar, craniofacial, or axillary hyperhidrosis. This technique interrupts signaling to the sweat glands by disrupting or destroying a portion of the sympathetic trunk at the thoracic level [96, 97]. The main complications are compensatory hyperhidrosis, Horner's syndrome, hemothorax, neuralgia, pneumothorax, and lesion in the phrenic nerve [47].

Glossary

Apocrine sweat glands Larger sweat glands that occur in hair follicles. They appear after puberty.

Apoeccrine sweat glands Contain morphological features common to the eccrine and apocrine sweat glands.

Eccrine sweat glands Small sweat glands that produce a fluid secretion without removing cytoplasm from the secreting cells and that are restricted to the human skin.

Hyperhidrosis Sweating greater than necessary for the maintenance of normal body thermoregulation.

Primary hyperhidrosis Excessive sweating in specific regions of the body and not caused by other medical conditions or by medications.

Secondary hyperhidrosis Excessive sweating caused by medications or medical conditions.

Sympathectomy Procedures that break the sympathetic innervation, thereby blocking stimulation of eccrine glands.

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Alopecia

68

Giselle Martins, Isabella Doche, Laura Freitag,
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Key Points Summary
- Knowledge about of different types of scarring and nonscarring alopecia is very important
- Dermoscopy and scalp biopsy are tools to aid the etiologic diagnosis of alopecia
- The treatment of alopecia must be individualized

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Concepts The word *alopecia* has been used to designate all kinds of hair loss; however, the most important differentiation is between scarring and nonscarring alopecia. This concept is important in helping to find the correct diagnosis and establish the prognosis.

Hair Shaft Disorders

Hair shaft abnormalities encompass a group of congenital or acquired alterations that can lead to variations in hair appearance, texture, density, and growth capacity with or without increased hair fragility [1]. These changes may be occasional findings or important clues for the diagnosis of systemic or localized disorders and genetic syndromes [2, 3].

Dermoscopy, optic microscopy, and polarized light microscopy of hair shafts, in addition to a complete anamnesis and physical examination, are essential to a correct diagnosis. To treat the cause and minimize hair shaft damage are the mean aims for these conditions.

Structural hair abnormalities associated with increased hair fragility comprise monilethrix, trichorrhexis invaginata, trichorrhexis nodosa, pili torti, and trichothiodystrophy. However, some hair shaft disorders are not associated with increased hair fragility, for example, pili annuati and woolly hair.

Monilethrix

Introduction and Etiopathogenesis Monilethrix is a rare hereditary autosomal dominant human hair disorder in which affected fragile hairs have a unique beaded morphology. It is caused by mutations in type II hair cortex keratins KRT86 (most of all), KRT81, and KRT83, and chromosome 12q13 [3]. In addition, autosomal recessive mutations have been found in the gene that encodes desmoglein 4.

Clinical Presentation and Diagnosis The monilethrix phenotype is variable even among members of the same family; in the mildest forms dystrophic hair may be confined to the occiput, but more severely affected individuals have near total alopecia [2]. Hair is usually normal at birth and is replaced with abnormal hair within the first few months of life. Hair is beaded and fragile, which tends to break at points of narrowing, thus leading to short, stubby hair, especially at the sites of friction such as the nape and occipital areas. In more extensive cases the eyebrows, eyelashes, pubic area, axillary area, arms, legs, and nails may be involved (especially koilonychia). Perifollicular erythema, follicular keratosis of the affected scalp, and keratosis pilaris are also typical [4, 5].

Dermoscopy shows hair abnormalities of terminal and vellus hair, with uniform and elliptical nodes and intermittent constrictions, leading to hair thickness variations [6]. The nodes are the normal diameter of the shaft and the internodes represent atrophic parts [2]. The hairs are bent at regular intervals and usually break in constricted areas [6], as seen in Fig. 68.1.

In the differential diagnosis pseudomonilethrix, pili torti, and "monilethrix-like" shafts must be excluded. Pseudomonilethrix is a developmental hair shaft defect characterized by irregular nodes along the hair shaft, with fragility and hair breakage resulting in partial baldness. No follicular papule can be seen. On electron microscopy, the pseudomonilethrix nodes appear to be an optical illusion, and the constriction sites show real indentations protruding beyond the normal shaft [2]. Monilethrix-like shafts show similar ovoid hair shaft constrictions without characteristic typical regularity. They can be found in alopecia areata and lichen planopilaris, and after chemotherapy [6].

Therapeutic Approach Counseling the patient and avoiding hair trauma represent the most effective treatment. Oral acitretin and topical minoxidil can help in some cases.

Trichorrhexis Invaginata

Introduction and Etiopathogenesis Trichorrhexis invaginata (bamboo hair) is a follicular abnormality with hair shaft fracture resulting from invagination of the shaft's distal portion into the proximal portion, due to a cornification defect. It is pathognomonic of Netherton syndrome, a rare autosomal recessive disease that combines ichthyosis linearis circumflexa, erythroderma, growth retardation, failure to thrive, and atopic state [2, 7]. The disorder results from mutation with function lost on the *SPINK5* gene, which codes LEKT1, a serine protease inhibitor [5].
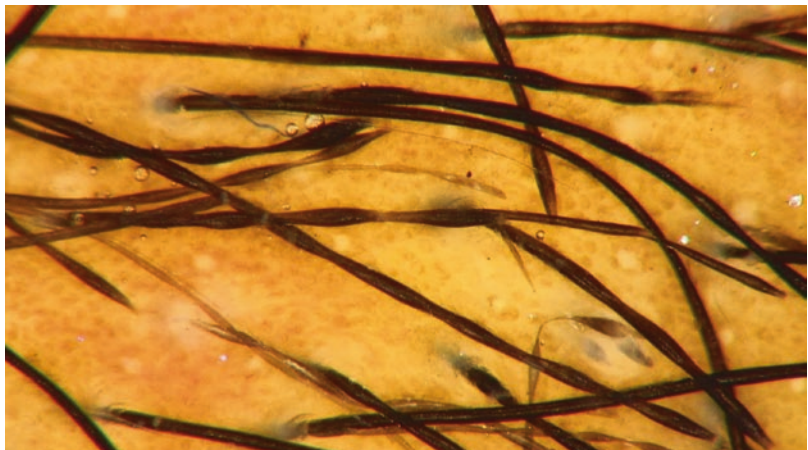
Fig. 68.1 Monilethrix: uniform elliptical nodes and intermittent constrictions (Courtesy of Dr. Giselle Martins Pinto, Porto Alegre, Brazil)

Clinical Features and Diagnosis The hair abnormality usually becomes evident in infancy, showing patchy hair thinning and sometimes complete alopecia. Eyelashes and eyebrows are sparse or absent [2]. Hair shafts tend to be dry, short, sharp, and brittle.

On dermoscopy, trichoscopy shows a hair shaft telescoping into itself (invagination) at several points along the shaft, typical of "bamboo hair" and "golf tee hair." At lower magnifications this may appear as nodular structures located along the hair shaft [8, 9].

The differential diagnosis includes trichorrhexis nodosa, monilethrix, and black piedra [9].

Therapeutic Approach Oral retinoid therapy seems to improve keratinization and hair appearance. In adults the scalp hair tends to improve, but the eyebrow and eyelash alterations tend to persist [2].

Trichorrhexis Nodosa

Introduction and Etiopathogenesis Trichorrhexis nodosa is the most common hair structure abnormality and is not specific for a disease. It consists of hair shaft fracture with splayed individual cortical cells, and their fragments resemble two brushes pushed together [2]. Most cases are acquired and are related to hair trauma or associated with genetic syndromes (i.e., Netherton syndrome, acrodermatitis enteropathica, biotinidase deficiency, argininosuccinic aciduria, citrullinemia, Menkes disease,

and ectodermal defects). Congenital trichorrhexis nodosa is rare.

Clinical Features and Diagnosis Hair shafts seem dry and brittle, with evident hair breaks leaving variable lengths of broken hair and even partial alopecia. There may be intense itching in the affected areas.

Dermoscopy at low magnification shows nodular thickening along hair shafts, which appear as light-colored nodules or gaps, as seen in Fig. 68.2a, b. High-magnification trichoscopy shows hair fibers with typical brush-like ends [8].

The differential diagnosis includes trichorrhexis invaginata, monilethrix, and black piedra.

Therapeutic Approach Reducing trauma and mild cosmetic procedures are the aspects essential to treatment. Early recognition and specific treatment of inherited causes are mandatory.

Pili Torti

Introduction and Etiopathogenesis In pili torti the hairs are flattened and, at irregular intervals, completely rotated through 180° around their long axis [10]. It can be associated with copper deficiency (i.e., Menkes disease) and ectodermal disorders [2]. This hair shaft disorder can be congenital, sporadic, or acquired.

Clinical Features and Diagnosis The classic, inherited, form can be autosomal dominant or
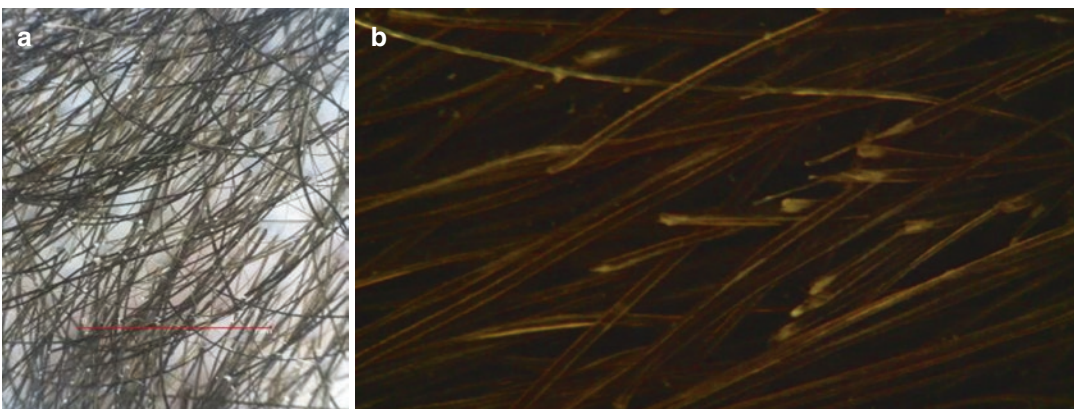
Fig. 68.2 (**a**, **b**) Trichorrhexis nodosa on dermoscopy: see the white structures along the hair shaft (Courtesy of Dr. Giselle Martins Pinto, Porto Alegre- Brazil)

recessive, beginning in childhood between the third month and third year of life. It is more common in blond-haired girls, and the typical appearance predominates at friction areas, especially temporal and occipital, occasionally affecting eyebrows and eyelashes [2, 11]. The later type, an autosomal dominant disorder, begins after puberty and involves predominately dark hairs. The acquired form of pili torti is related to repetitive trauma, oral retinoids, cicatricial alopecia, and scleroderma. Menkes disease, or trichopoliodystrophy, is a lethal X-linked disease of copper metabolism caused by mutations in ATP7A, a gene that encodes a copper-transporting ATPase. It affects males with classical pili torti, neurodegenerative symptoms, and connective tissue disturbances. Hair is sparse in density, depigmented, lusterless, and feels like steel wool [5]. The most important clue is a marked reduction in blood copper and ceruloplasmin levels. However, these levels may be normal within the first weeks of age, with great reduction after the fourth week [2]. Hair is brittle and breaks easily at different lengths with a spangled appearance in reflected light. There may be only a short coarse stable or circumscribed baldness, irregularly patchy or occipital. The scalp area, less subject to trauma, can be spared [10].

Dermoscopy at high magnification light microscopy reveals a flattened hair shaft twisted through 180° on its own longitudinal axis, irregularly along the hair shaft. Only some shafts and some parts of shafts are affected.

The main differential diagnosis is Bjornstad syndrome, an autosomal recessive disease caused by mutation of the gene BCSIL with associated pili torti and neurosensorial deafness. Isolated twisted hairs can be found in a normal scalp [2].

Therapeutic Approach The conditions usually improve after puberty. Patients should avoid additional traumas. Menkes disease has a poor prognosis and most of the patients die within the first 3 years of life. When diagnosis have been made early, especially before neurologic manifestation, copper-histidine injection may be useful to a certain extent [2].

Pili Annulati

Introduction and Etiopathogenesis Pili annulati is a hair shaft disorder that causes a distinct appearance of the hair with intermittent light and dark bands [2]. The condition may be sporadic or autosomal dominant, and the genetic defect maps to chromosome 12q [11].

Clinical Features and Diagnosis Pili annulati is visualized at birth or in the first year of age. Hair appears bright and without increased fragility, and there may be some additional fragility at lighter areas. The bright bands are subtle, opaque, and shorter than dark bands. Usually 20–80% of hairs are affected. The bright appearance of the bands is due to air-filled cavities within the cortex that scatter the light [2]. Lighter areas extend to 50–100% hair thickness [11, 12].

Trichoscopy shows hair shafts with alternate light and dark bands. In other respects, hair is normal.

For the differential diagnosis, pseudopili annulati is a condition where the alternate-band clinical appearance is an optical effect caused by partial twisting of the hair shaft. Pili torti and fragmented or intermittent medulla must be excluded.

Therapeutic Approach Generally treatment is not necessary, although avoidance of additional hair trauma is desirable.

Trichothiodystrophy

Introduction and Etiopathogenesis The term trichothiodystrophy (TTD) covers a range of phenotypes, with low-sulfur, fragile hair representing the central defining criterion [10]. This is a neuroectodermal complex disturbance, with heterogeneous clinical manifestations and autosomal recessive inheritance. Currently there are three disease types: (1) the photosensitive type, which has mutation at genes encoding transcription-DNA factor IIH (TFIIH) subunits (XPD, XPB, p8/TTDA); (2) the nonphotosensitive type with TTDN1 mutation, and (3) the nonphotosensitive

type without TTDN1 mutation and without known genetic basis [11, 13, 14].

Clinical Features and Diagnosis Patients with TTD share the distinctive features of short, sparse, and brittle hair and variable degrees of alopecia. The abnormalities are inversely proportional to the sulfur content. Trauma may lead to transverse break (trichoschisis) or nodes resembling trichorrhexis nodosa [2, 10]. The presence of low sulfur content in hairs and one of trichoschisis, tiger-tail pattern by polarizing light microscopy, or severe cuticular damage are mandatory for diagnosing TTD [2]. Clinical features are variable; persistent alopecia is often found and other body hairs may be affected. Physical and mental impaired and nail and dental dysplasia are frequent. TTD syndromes include BIDS (Brittle hair, Intellectual impairment with low IQ, Decreased fertility, Short stature) and the variants PIBDS (BIDS plus Photosensitivity and ichthyosis) and IBIDS (BIDS with ichthyosis).

Trichoscopy has limited value in TTD, although sometimes it can show trichoschisis. The diagnosis is made by polarizing light microscopy, with the tiger-tail pattern with alternating light and dark bands along the hair shaft. This is not a specific signal but highly suspicious.

For the differential diagnosis, any hair shaft disease associated with increased hair fragility, such as monilethrix, must be considered.

Therapeutic Approach There is no specific treatment. In photosensitive types it is important to avoid solar exposure.

Woolly Hair

Introduction and Etiopathogenesis Woolly hair is a structural hair abnormality not associated with increased hair fragility. It can occur over the entire scalp or part of it as a woolly hair nevus [10]. Its inheritance may be congenital, autosomal dominant, or recessive.

Clinical Features and Diagnosis Tight coiling, fractures, and knots are common. Microscopic examination reveals ovoid or elliptical cross-sections and 180° axial twisting of the hair shaft. Woolly hair is found in association with palmoplantar keratoderma and cardiomyopathy syndromes: Naxos (mutation in the gene for plakoglobin) and Carvajal (mutation in the gene for desmoplakin). In addition, there are autosomal dominant forms associated with ichthyosis and deafness, an acquired type, and a localized woolly hair nevus, a nevoid condition showing different hair texture and color [10].

Trichoscopy demonstrates a hair shaft with waves at very short intervals. The appearance of variable hair shaft thickness results from twists [6].

As differential diagnoses one must consider trichorrhexis nodosa and pili annulati, which sometimes can coexist.

Therapeutic Approach There is no specific treatment.

Inflammatory Scalp Diseases

Psoriasis

Introduction and Etiopathogenesis Psoriasis is a very common inflammatory skin dermatosis affecting 2–3% of the general population. Although the scalp is frequently affected in this condition, few reports of permanent alopecia have been described to date [15, 16]. Itching and scaling are very frequent and can be the sole presentation of the disease, making it difficult to differentiate from seborrheic dermatitis. The precise pathogenesis of psoriasis is unknown [17]. Similarly to other autoimmune diseases, a complex interaction of genetic and environmental factors leading to self-sustained and chronic immune response seems to be critical. Scales are a result of hyperproliferative status of the epidermis with premature maturation of keratinocytes and incomplete cornification, with retention of nuclei in the stratum corneum [18]. More recently, the role of some lipid mediators and neuropeptides, such as substance P, have been studied in the setting of this disease [19, 20].

Clinical Features and Diagnosis Alopecia may be directly related to the psoriasis itself, and can affect both the scalp and other parts of the body. It is characterized by sharply circumscribed erythematosquamous plaques with silvery scales usually extending over the hairline (Fig. 68.3). Immunocompromised patients may present more severe lesions. Psoriatic alopecia most commonly affects lesional skin, but may present as a generalized telogen effluvium. In most cases there is regrowth of hair, but in rare cases it can cause scarring alopecia.

Regarding pathology, classic plaques of scalp psoriasis show psoriasiform acanthosis (regular hyperplasia) with confluent parakeratosis, neutrophils in the stratum corneum (Munro microabscesses), and dilated vessels with perivascular infiltrate in the upper dermis. Necrotic keratinocytes can be found in the epidermis. The sebaceous glands show atrophy and present as epithelial stands of underdeveloped lobules (mantle structures), as seen on Fig. 68.4 [21].
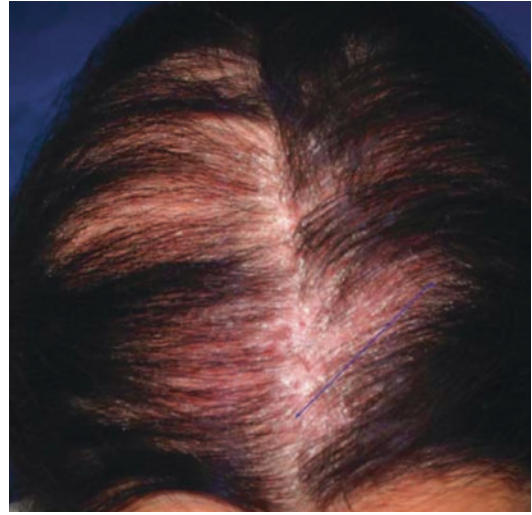
Fig. 68.3 Psoriatic alopecia: erythema, scales, and decreased hair density (Courtesy of the Division of Dermatology, Hospital das Clinicas, University of São Paulo, Brazil)
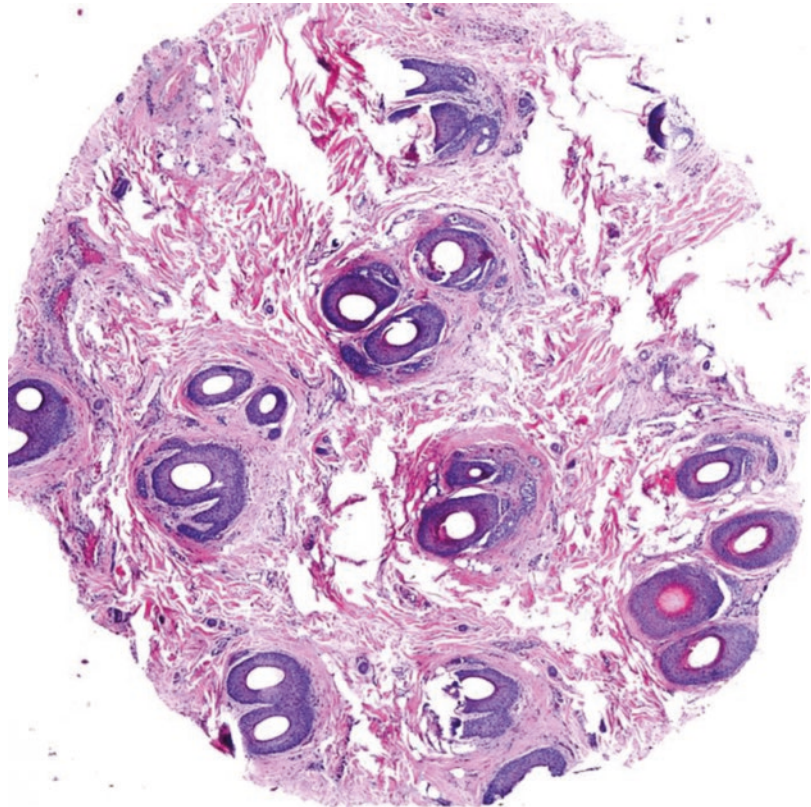
Fig. 68.4 Scalp psoriasis: horizontal sections at the isthmus level. The sebaceous glands are absent and replaced by mantle structures (Courtesy of Dr. Maria Miteva Pinto, Miami, USA)

Since telogen effluvium is a common presentation in scalp psoriasis, there is an increased telogen count in horizontal sections. Prominent eosinophils and plasma cells have been found in scalp biopsies of patients who developed psoriatic alopecia (alopecia areata like) reactions after treatment with tumor necrosis factor α (TNF-α) inhibitors [22].

Dermoscopy of psoriatic alopecia shows interfollicular twisted red loops characteristic of scalp psoriasis, and lack of follicular openings (Fig. 68.5). Silvery scales with keratin casts along the hair shafts can also be noted.

In the differential diagnosis, other causes of flacking include seborrheic dermatitis, contact dermatitis, tinea capitis, and pityriasis amiantacea. Other infrequent conditions include ichthyosis, pityriasis rubra pilaris, zinc deficiency, Langerhans cell histiocytosis, and Wiskott–Aldrich syndrome [23].

Therapeutic Approach Various topical treatment options including steroids, keratolytic agents, and coal tar, and calcineurin inhibitors are available for scalp psoriasis [24]. In some cases, psoriasis treatments may also contribute to hair loss. Application of topical preparations may cause hair loss through friction, and many of the systemic treatments used for psoriasis can also cause hair problems. Treatment with anti-TNF-α agents can precipitate de novo psoriasis and subsequent psoriatic alopecia [25].

Seborrheic Dermatitis

Introduction and Etiopathogenesis Seborrheic dermatitis (SD) is an inflammatory condition of the skin which affects 1–3% of immunocompetent adults [26]. It is more frequent in adolescents and young adults, although a high incidence can be noted in patients older than 50 years. Typical lesions commonly occur on the scalp, face, and chest. SD can worsen during winter time and be more prevalent in patients with immunodeficiencies and neurologic conditions. Dandruff is a mild presentation of the disease, resulting in fine scaling of the scalp. The cause of SD is unknown. Many factors such as sebum production, *Malassezia* sp. colonization, and individual immune response are thought to play an important role in its pathogenesis. The current understanding of dandruff is that while some degree of increased cell turnover may contribute to the amount of flaking, this is not a primary hyperproliferative condition. Rather, any increased cell production is a consequence of inflammation [27].

Fig. 68.5 Scalp psoriasis: area of interfollicular twisted red loops (Courtesy of the Division of Dermatology, Hospital das Clinicas, University of São Paulo, Brazil)

Clinical Features and Diagnosis Clinical lesions of SD are characterized by yellowish moist scales over the scalp, and oily areas such as eyebrows, sideburns, and beard, and alar, nasolabial, and postauricular creases. Variable erythema and pruritus may occur. Dandruff is marked by white-grayish tiny flakes that can accumulate and fall from the scalp onto the shoulders. Usually it is not inflamed or pruritic.

In dermoscopy, the most specific trichoscopic features of scalp SD are multiple thin arborizing vessels and yellowish perifollicular and interfollicular scaling (Fig. 68.6) [28, 29].

Regarding pathology, classic SD is rarely biopsied for diagnostic purposes. It may be encountered as a concomitant finding in the scalp biopsies from patients with other primary hair disorders. The main findings are acanthosis (sometimes psoriasiform) with spongiosis and peri-infundibular (shoulder) parakeratosis (Fig. 68.7). There is mild perivascular lymphocytic infiltrate in the upper dermis. Yeast

Fig. 68.6 Seborrheic dermatitis: yellowish perifollicular and interfollicular scaling (Courtesy of Dr. Patricia Damasco, Brasilia, Brazil)

Fig. 68.7 Seborrheic dermatitis: psoriasiform acanthosis with parakeratosis mostly in perinfundibular pattern (Courtesy of Dr. Maria Miteva, Miami, USA)
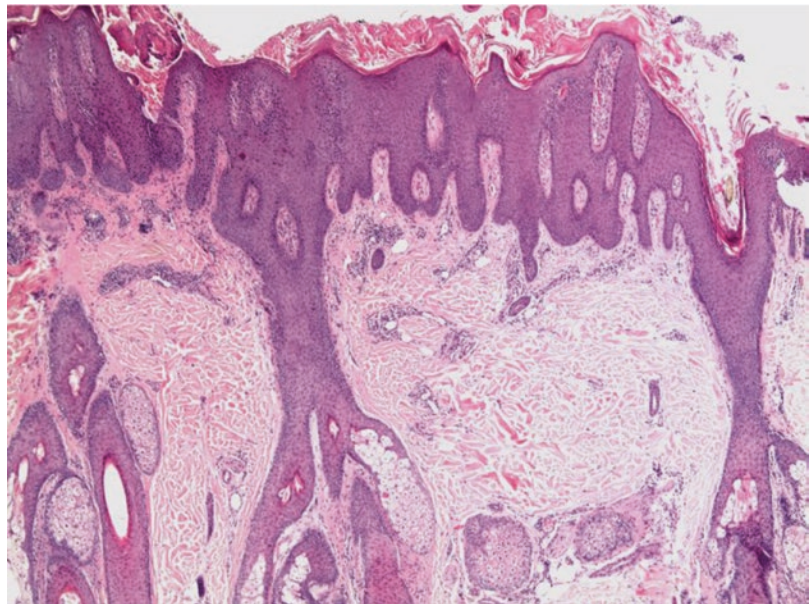
Fig. 68.8 Seborrheic dermatitis: horizontal section at the level above the isthmus. Note dilated sebaceous canals, spongiosis and parakeratosis in the follicular epithelium, as well as lymphocytic inflammatory infiltrate (Courtesy of Dr. Maria Miteva, Miami, USA)
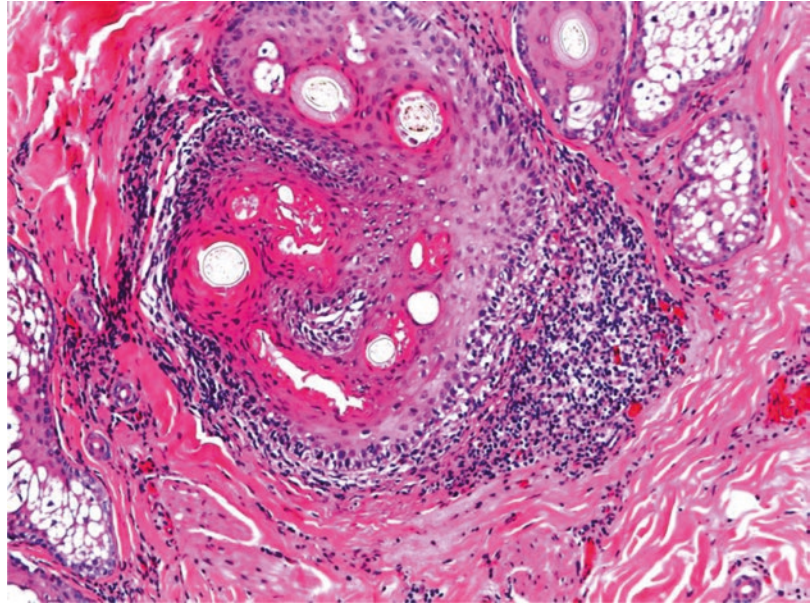
Table 68.1 Treatment of seborrheic dermatitis

Antidandruff and antiseborrheic shampoos (ketoconazole, ciclopirox, selenium sulfide, zinc pyrithione, coal tar)
Topical keratolytics (salicylic acid or urea)
Topical antifungal medications (miconazole or ketoconazole)
Topical low-potency steroids (hydrocortisone, betamethasone, mometasone)
Topical calcineurin inhibitors (tacrolimus, pimecrolimus)
Oral ketoconazole, itraconazole, or terbinafine

forms of *Pityrosporum* can be found in the stratum corneum. The sebaceous ducts are dilated and the sebaceous glands show hypertrophy (Fig. 68.8).

The clinical differential diagnosis includes psoriasis, atopic dermatitis, tinea capitis, discoid lupus erythematosus, and contact dermatitis.

Therapeutic Approach Although there is no cure for SD, patients may be aware that this is a relapsing condition that may require maintenance treatment. SD can be treated with a large number of agents such as antidandruff shampoos, topical low-potency steroids, and oral therapy for resistant cases, as seen in Table 68.1 [30].

Infections Scalp Disease

Syphilitic Alopecia

Introduction and Etiopathogenesis Syphilis is a chronic systemic, sexually transmitted infection caused by the spirochete *Treponema pallidum*. Syphilis can mimic many diseases through its pattern of scalp alopecia. Alopecia is an uncommon clinical manifestation of secondary syphilis, ranging from 2.9% to 7% [31]. The precise pathogenesis of this condition is still unknown. The spirochetes pass through the mucous membranes or minor abrasions of the skin to the lymphatics and bloodstream within a few hours of inoculation. After local proliferation of the causative agent, there is formation of chancre, the primary lesion of the disease. Usually the lesion is rarely noted and cellular immunity results in healing of this primary stage. If not treated, the disseminated organisms result in the late stages of the disease, with essentially underlying vasculitis.

Clinical Features and Diagnosis Syphilitic alopecia can present patterned hair loss such as "moth-eaten," diffuse, or both. The "moth-eaten" pattern is the most common type and is considered

to be a pathognomonic manifestation of secondary syphilis [31–33]. The alopecia, which is nonscarring, can occasionally affect hair-bearing areas other than scalp [31, 33]. Alopecia syphilitica often is associated with other mucocutaneous symptoms of secondary syphilis, but the hair loss as a unique clinical presentation is extremely rare [32]. Two basic patterns of secondary syphilitic alopecia have been described in the literature, symptomatic and essential syphilitic alopecia. The first type presents with either a patchy or diffuse pattern associated with skin lesions of secondary syphilis on the scalp or elsewhere over the body (Fig. 68.9). However, the essential alopecia has the same hair loss pattern as symptomatic alopecia but without any other cutaneous feature of syphilis [33].

In dermoscopy, trichoscopic features in syphilitic alopecia are unspecific with few reports in the literature. Decreased hair density, yellow dots, and broken hairs are the most frequent findings [34, 35]. The lack of specific markers such as "exclamation-mark" hairs and comma hairs on trichoscopy can help to rule out alopecia areata and tinea capitis.

Pathologically, in a scalp biopsy from the moth-eaten-like patches of nonscarring alopecia in secondary syphilis there is a markedly reduced number of anagen follicles and an increased number of catagen and telogen follicles [36]. The pathology can be indistinguishable from acute-stage alopecia areata, as the presence of peribulbar lymphocytic infiltrate has been observed in both. Scattered plasma cells when present may indicate the diagnosis. Immunohistochemistry can highlight the *T. pallidum* in in the hair follicles, usually in the perifollicular and peribulbar regions, and helps in the diagnosis.

For the differential diagnosis, syphilitic alopecia can mimic alopecia areata both on clinical and histopathologic examinations [32, 37]. Trichotillomania, tinea capitis, and systemic lupus must be excluded as well. Serologic treponemic tests are fundamental to confirm the disease. It is important to include syphilitic alopecia as a cause of diffuse hair shedding.

Therapeutic Approach Penicillin is the drug of choice for treating all stages of syphilis. A single shot of 2.4 million units of benzathine penicillin

Fig. 68.9 Syphilis: diffuse pattern of alopecia in a patient with secondary syphilis (Courtesy of the Division of Dermatology, Hospital das Clinicas, University of Sao Paulo, Brazil)

G is highly effective for the treatment of primary and secondary infection. In cases of penicillin allergy, tetracycline hydrochloride, 500 mg every 6 h or doxycycline 100 mg, twice daily for 15 days can be used. Treatment for late latent syphilis, tertiary syphilis, or latent disease of unknown duration require a longer duration of therapy.

Tinea Capitis

Introduction and Etiopathogenesis Tinea capitis is a fungal infection that usually affects children between the ages of 4 and 7 years and immunocompromised individuals. Nowadays, the etiology and pattern of the lesions are considered to vary with age, as well with gender and general health condition. The incidence of tinea capitis in the general population seems to be increasing, particularly among African American children who account for more than 80% of the cases [38]. The epidemiology of this disease varies widely, ranging from antropophilic, zoophilic, and geophilic dermatophytes. The main causative organisms of tinea capitis belong to two genera, *Microsporum* and *Trichophyton*, although the organisms responsible for superficial scalp fungal infections also vary considerably with geography [39]. Dermatophytes cause superficial fungal infections by the attachment of the hyphae to the keratinized surfaces including the perifollicular stratum corneum. The organism produces arthroconidia after it easily penetrates the cortex of the hair by way of keratinase enzymes. The hairs that are filled with arthroconidia become fragile and tend to break at the surface of the scalp. Microscopically, ectothrix arthroconidia can be observed in the surface of plucked hairs, while endothrix arthroconidia are localized within the hair shaft.

Clinical Features and Diagnosis The pattern of clinical findings with tinea capitis infection depends on the causative organism and the host inflammatory response. The most common presentation is single or multiple patches of alopecia associated with variable inflammation, scale, and pruritus (Fig. 68.10). Special forms of tinea capi-

tis are kerion celsi and favus. Kerion celsi is a highly inflammatory and suppurative form of tinea capitis, usually caused by zoophilic fungi. It can cause scarring alopecia if not aggressively treated. Favus, also known as tinea favosa, is a rare but severe presentation of tinea capitis, characterized by the chronic fungal infection in endemic regions. In the late phase of the disease it can also cause scarring hair loss. The diagnosis of tinea capitis is based on microscopic examination of infected hairs. Mycologic culture is fundamental for a precise identification of the causative organism. Wood's lamp examination may also be useful in some forms of tinea (Table 68.2).

Dermoscopy is an inexpensive and useful tool that can provide an easy and rapid diagnosis of tinea capitis. The presence of specific trichoscopy features, such as comma and corkscrew hairs, may help to differentiate tinea capitis from other scalp conditions (Fig. 68.11). Comma hairs may be found in both endothrix and ectothrix

Fig. 68.10 Tinea capitis: inflammation and pustules on the scalp (Courtesy of Dr. Giselle Martins Pinto, Porto Alegre, Brazil)

infections [40]. Corkscrew hairs were first described in black patients with *Trichophyton soudanense*, although a recent publication described this finding in a white adult patient [41, 42]. Broken hairs, although very common, are not specific and may be present also in trichotillomania, chemotherapy, and alopecia areata [43].

Table 68.2 Hair invasion patterns of dermatophytes

Ectothrix infections
Most common organisms: *Microsporum* spp. and *Trichophyton rubrum*
Clinical presentation: annular scaling plaque with less inflammation and scale
Wood's lamp fluorescence: fluorescent (*Microsporum* spp.) or nonfluorescent (*T. rubrum* and *Microsporum gypseum*)
Endothrix infections
Most common organisms: *Trichophyton* spp.
Clinical presentation: multiple plaques with less inflammation and scale
Wood's lamp fluorescence: nonfluorescent
Kerion celsi
Most common organisms: *T. verrucosum*, *T. mentagrophytes*, and *M. gypseum*
Clinical presentation: suppurative, boggy, nodular deep folliculitis with fistulas and pus secretion. Regional lymphadenopathy, fever, and headache may occur
Wood's lamp fluorescence: nonfluorescent
Favus
Most common organisms: *T. schoenleinii*
Clinical presentation: presence of scutulas (small, yellow, scaly crusts) with musky odor. Purulent discharge may occur
Wood's lamp fluorescence: fluorescent

Pathologically, in tinea capitis caused by ectothrix infection (*Mycobacterium canis*) the hyphae and spores cover the outside surface of the hair shaft, which results in destruction of the cuticle. In tinea capitis caused by endothrix infection (*Trichophyton tonsurans*), the inside of the hair shaft is invaded only by rounded and box like arthrospores and not by hyphae (Fig. 68.12).

In inflammatory tinea capitis (kerion) caused by *M. canis*, *T. mentagrophytes*, *T. tonsurans*, *T. rubrum*, and *M. gypseum*, there is dense mixed cell inflammatory infiltrate of neutrophils, plasma cells, eosinophils, lymphocytes, and histiocytes as well as giant cells. The infiltrate involves the follicles and the surrounding dermis and subdermis (suppurative granulomatous folliculitis) (Fig. 68.13). The special stains may be falsely negative [44].

The differential diagnosis of many scalp conditions may mimic tinea capitis, including SD, atopic dermatitis, psoriasis, and trichotillomania. Alopecia areata typically presents as bare scalp patches with no erythema or scale. Pustular and inflamed lesions may rule out bacterial infections and decalvans folliculitis. Dissecting folliculitis may also resemble tinea capitis, but the lack of comma hairs and follicular ostia may lead to the correct diagnosis.

Therapeutic Approach Systemic antifungals should be initiated upon clinical suspicion of tinea capitis, as topical medications alone are ineffective. The most effective drugs are griseofulvin, terbinafine, and the azoles (Table 68.3).

Fig. 68.11 Tinea capitis: dermoscopy shows corkscrew hairs and broken hairs (Courtesy of Dr. Giselle Martins Pinto, Porto Alegre, Brazil)

Fig. 68.12 Inflammatory tinea capitis: horizontal sections at the level of the bulb: there is dense (abscess like) mixed cell infiltrate which extends from the bottom to the surface (Courtesy of Dr. Maria Miteva, Miami, USA)
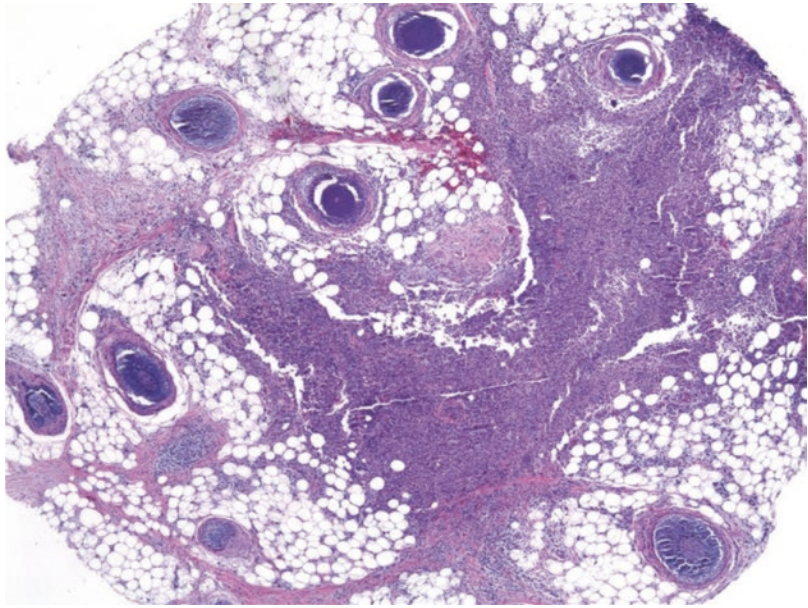
Fig. 68.13 Tinea capitis: the hair shaft is loaded with fungal spores (Courtesy of Dr. Maria Miteva, Miami, USA)
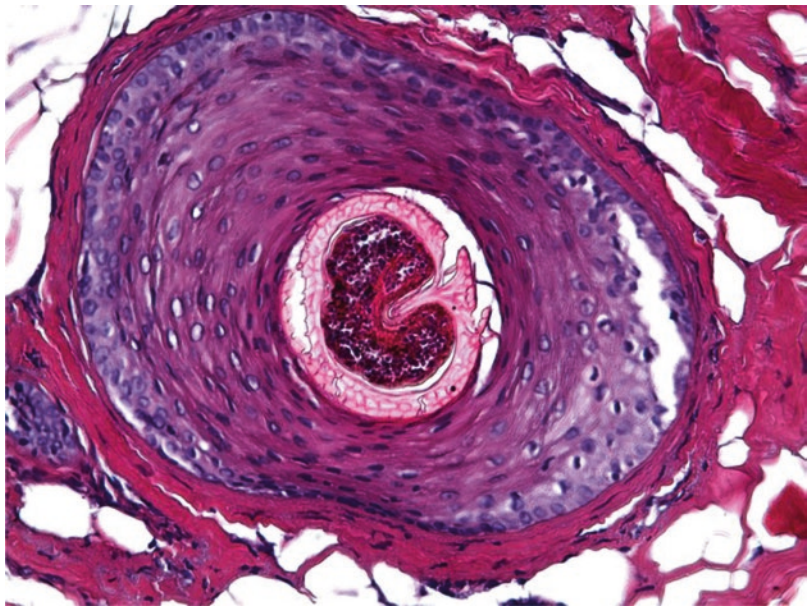
Topical medications such as ketoconazole 2% and zinc pyrithione 1% shampoos should be used to decrease the viability of fungal spores present on the hair, as well as for all household contacts, to prevent infection or eliminate the carrier state [45]. Children can return to school once appropriate treatment has been initiated. Personal hair items should be disinfected or discarded. If a zoophilic organism is isolated, cats and pets should also be treated. Kerion celsi may require oral steroids in the management of inflammation if no response is achieved after 2 weeks of systemic antifungal therapy. Tinea favosa requires that all family members should be treated simultaneously because of its chronic and endemic infection pattern.

Table 68.3 Systemic drugs used for the treatment of tinea capitis

Griseofulvin (first-line therapy for adults and children)
Dosage: 10–15 mg/kg/day (maximum: 500 mg/day) or 20–25 mg/kg/day for microsized formulation
Duration: 6–8 weeks/ continue 2 weeks after resolution of the lesions
Side effects: headache, gastrointestinal discomfort and, rarely, rash and elevated liver enzymes
Notes: better absorption with fatty meals. Eczematous id reaction may occasionally occur in the beginning of the treatment
Terbinafine
Dosage: 3–6 mg/kg/day based on weight
10–20 kg: 62.5 mg/day
20–40 kg: 125 mg/day
>40 kg: 250 mg/day
Duration: 2–4 weeks continuously or 2–4 1-week pulses, 3–4 weeks between pulses
Side effects: headache, gastrointestinal discomfort, rash
Notes: *M. canis* may require longer course
Itraconazole
Dosage: 5 mg/kg/day in capsules
Duration: 2–4 weeks continuously or 2–4 1-week pulses, 2–3 weeks between pulses
Side effects: headache, gastrointestinal discomfort, rash, dysgeusia
Note: Capsules should be taken with food for better absorption. *M. canis* may require longer course. Suspension is not recommended as it has shown increased incidence of pancreatic adenocarcinomas in rats
Fluconazole
Dosage: 6 mg/kg/day
Duration: 2–4 weeks
Side effects: headache and gastrointestinal discomfort
Note: Absorption not affected by the presence of the food

Acquired Nonscarring Alopecia

Acute Telogen Effluvium

Introduction and Etiopathogenesis This condition was first described by Kligman in 1961, as an acute and diffuse hair loss due to a variety of triggers [46]. The normal hair follicle activity is cyclical, consisting of anagen (hair growth phase), catagen (involution phase), telogen (resting phase), and exogen (release phase occurring in late telogen or early anagen) [47]. On the scalp, hairs remain in anagen for 2–6 years, whereas telogen lasts for approximately 100 days [48]. An average normal scalp has 100,000 hairs, with approximately 85% being in anagen, 15% in telogen, and only a few follicles in the transitional or catagen phase [48]. By definition, telogen effluvium (TE) is a nonscarring, diffuse hair loss from the scalp that occurs around 3 months after a triggering event, and is usually self-limiting within 6 months [48]. TE occurs if a significant number of anagen hairs are triggered to stop growing prematurely by any stimulus and subsequently enter catagen phase, followed by telogen phase. After about 2–3 months there is excessive hair shedding [49]. A wide variety of potential triggers have been implicated in the pathogenesis of TE. Postfebrile, postpartum, crash diet, drugs (oral contraceptives, antithyroid drugs, anticonvulsants, β-blockers, oral retinoids), and severe emotional distress are among the most common causes [50].

There are five functional types of TE described by Headington [48].

1. Immediate anagen release, whereby the follicles are stimulated to leave anagen and enter telogen prematurely, resulting in increased TE 2–3 months later. This can accompany physiologic stress, severe illness, and drug-induced hair loss.
2. Delayed anagen release due to prolongation of anagen, resulting in delayed but synchronous onset of heavy telogen shedding. This type typically occurs in postpartum hair loss (telogen gravidarum) or after discontinuation of contraceptive pills.
3. Immediate telogen release occurs with drug-induced shortening of telogen, leading to follicles re-entering anagen prematurely. This type of hair shedding usually occurs 2–8 weeks after initiation of therapy with minoxidil.
4. Short anagen syndrome is characterized by inability to grow long hair because of an idiopathic short anagen phase.

5. Delayed telogen release is characterized by prolonged telogen and delayed transition to anagen. This may be responsible for seasonal hair loss in humans.

Clinical Features and Diagnosis Patients generally present with complaints of visible and diffuse increased hair loss. It can produce thinning of hair all over the scalp and bitemporal recession. Loss is normally not more than 50% of the scalp hair, and the daily rate of shedding can be up to 300 hairs [48].

Dermoscopically, trichoscopy has limited value in diagnosing effluvium. Frequent findings include the presence of empty hair follicles, peripilar sign (perifollicular discoloration), upright regrowing hairs (Fig. 68.14), and increase of follicular units within one hair. The frontal and occipital areas show no significant difference on the trichoscopy findings [51].

Differential diagnosis of TE must include androgenetic alopecia, diffuse alopecia areata, and psychogenic pseudoeffluvium.

Pathologically, the diagnosis of nonscarring alopecia requires horizontal sections of 4-mm punch biopsies. The horizontal sections provide the pathologist with an overview of the follicular architecture and follicular counts performed at several levels from the bulb to the infundibulum [52]. Nonscarring alopecia is characterized by preserved follicular architecture; the follicular units are composed of terminal and vellus follicles and sebaceous glands [53]. Acute TE is rarely biopsied since the condition is self-resolving. There is an increase in telogen count of more than 15%.

Therapeutic Approach Detailed history and clinical examination help to detect the cause of TE. If the cause is not obvious from the patient's history, iron studies, thyroid function tests, syphilis serology, and antinuclear antibody titer should be performed [48]. The most important aspect in the management of TE is counseling the patient about the natural history of the condition. Attempts should be made at identifying and correcting the cause. Hair shedding takes 3–6 months to stop, after which regrowth can be noted 3–6 months after removal of the trigger.

Chronic Telogen Effluvium

Introduction and Etiopathogenesis Chronic telogen effluvium (CTE) presents as a diffuse shedding of telogen hairs that persists more than 6 months. Although some cases of CTE may follow acute telogen effluvium with a known trigger, in most cases a specific trigger cannot be identified [53]. The pathogenesis of CTE is unknown,

Fig. 68.14 Telogen effluvium: upright regrowing hair and follicle unites with one hair. Note that the terminal hairs are uniform in thickness (Courtesy of Dr. Patricia Damasco, Brasilia, Brazil)

although it has been suggested that it is due to a reduction in the duration of anagen growth phase without hair follicle miniaturization [54, 55].

Clinical Features and Diagnosis Features include an insidious onset and a fluctuating course lasting for several years [55]. It typically affects middle-aged women. On examination there is some bitemporal recession and a positive hair-pull test equally over the vertex and occiput [48]. There is no widening of the central part, and shorter regrowing hairs can be noted in the frontal and bitemporal areas [47]. It is important to reassure patients that this condition represents exaggerated shedding rather than actual hair loss.

Dermoscopy produces results similar to those for acute TE.

Pathologically, a scalp biopsy from CTE is indistinguishable from the normal scalp. There is no or a slight decrease in the number of hairs with normal, and even increased terminal/vellus ratio of 9:1, as well as normal telogen count (up to 15%) [55] (Fig. 68.15).

Differential diagnosis includes androgenetic alopecia, diffuse alopecia areata, psychogenic pseudoeffluvium, and acute TE.

Therapeutic Approach The condition can spontaneously resolve after a decade or so [56].

Alopecia Areata

Introduction and Etiopathogenesis Alopecia areata is an autoimmune disease that presents as a nonscarring hair loss affecting children and adults [57]. Even though it is potentially reversible, it can lead to complete baldness of the scalp and the entire body. In the United States, alopecia areata was estimated to occur in 0.1–0.2% of the general population [57]. Although the exact pathogenesis of the disease remains to be clarified, the genetics of an individual may play roles at multiple levels in the development of alopecia areata. It is regarded as a T-cell-mediated autoimmune disease of the hair follicle
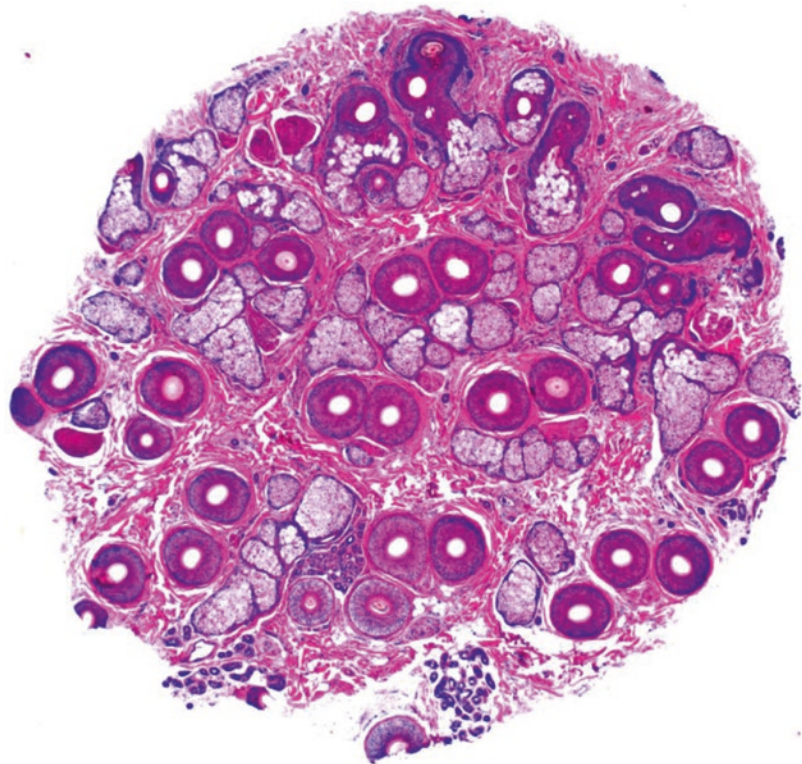
Fig. 68.15 Chronic telogen effluvium: horizontal section at the isthmus level. There is preserved follicular architecture. There are 34 terminal follicles and 3 vellus follicles (terminal/vellus ratio 11:1). The telogen count is 3% (Courtesy of Dr. Maria Miteva, Miami, USA)

that is mediated by CD4+ and CD8+ T lymphocytes. Alopecia areata most likely has a polygenic character, whereby susceptibility is dictated by several major genes and the phenotype may be modified by numerous minor genes [58]. An association with other autoimmune diseases has also been reported, such as thyroiditis and atopy [59]. Coexpression of vitiligo and alopecia areata has also been reported at between 4% and 9% [58].

Clinical Features and Diagnosis Alopecia areata can occur virtually in any hair-bearing area, affecting more commonly the scalp. It can present as single or multiple delimited patches of hair loss or diffuse scalp alopecia. In alopecia totalis there is a 100% loss of scalp hair, and if it involves additionally body hair it is called alopecia universalis [57, 59]. The pattern hair loss observed in alopecia areata can vary, including: reticular patches of hair loss; ophiasis type (band-like hair loss in parieto-temporo-occipital area); sisaipho type (reverse of ophiasis pattern, occurring on fronto-parieto-temporal area); and the diffuse variant of alopecia areata, characterized by global decrease in scalp hair density.

Classic alopecia areata lesions are circular patches of hair loss without any accompanying symptoms. The skin is usually normal on examination, but it is not uncommon to see slightly peach or reddened color [60]. The course is unpredictable and typically characterized by phases of acute hair loss followed by spontaneous hair regrowth. However, in severe forms hair loss can persist for many years (Fig. 68.16) [58].

Nail involvement may be observed in alopecia areata, and includes trachyonychia, Beau lines, transverse leukonychia, and red spotted lunulae [61].

Dermoscopically, the features of alopecia areata are regularly distributed yellow dots, micro-exclamation-mark hairs (Fig. 68.17), tapered hairs, black dots, broken hairs, and regrowing upright or regrowing coiled hairs (Fig. 68.3). Depending on disease activity, severity, and duration, the trichoscopic findings may differ [62]. Black dots, tapered hairs, and broken hairs correlates positively with disease activity [63]. Pohl–Pinkus constrictions with variable activity can be seen during the course of a disease (Fig. 68.18).

Pathologically, the findings in alopecia areata depend on the stage of the disease. In acute-stage alopecia areata there is peribulbar lymphocytic infiltrate ("swarm of bees") around terminal follicles in early episodes and around vellus follicles in repeated episodes (Fig. 68.19a) [64]. The infiltrate is composed of both CD4+ and CD8+ T-cell lymphocytes, with CD8+ NKG2D+ T-cell lymphocytes being the predominant portion. In subacute alopecia areata, there is decreased follicular

Fig. 68.16 Alopecia areata: multiple patches of hair loss on the scalp (Courtesy of Dr. Patricia Damasco, Brasilia, Brazil)

Fig. 68.17 Alopecia areata: micro-exclamation-mark hairs in alopecia areata (*white arrow*). These hairs are thin at the proximal end and thicker at the distal end (Courtesy of Dr. Patricia Damasco, Brasilia, Brazil)

Fig. 68.18 Alopecia areata: black dots, Pohl–Pinkus constrictions, and regrowing upright hairs (Courtesy of Dr. Patricia Damasco, Brasilia, Brazil)
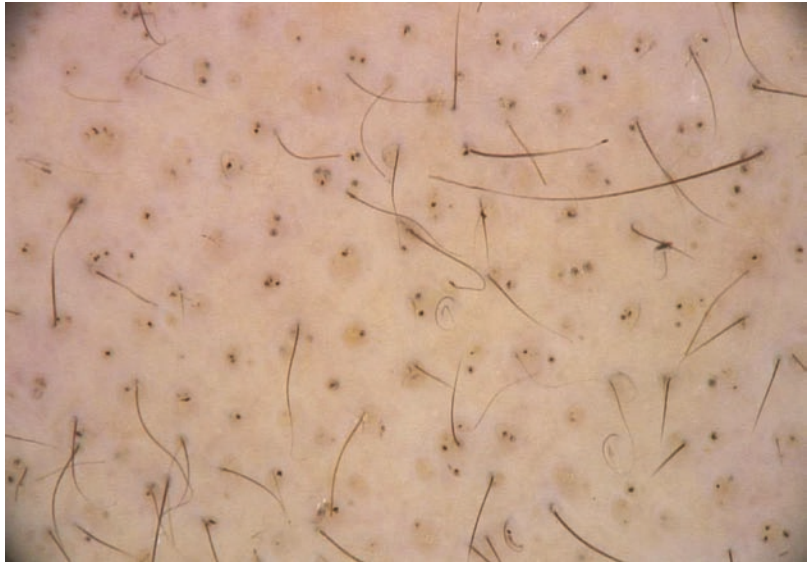
density with a reduced number of anagen and increased number of telogen follicles. The telogen count may be significantly increased, and is composed of catagen and telogen follicles and telogen germinal units (Fig. 68.19b). In the chronic stage there is a decreased number of terminal and an increased number of miniaturized follicles (decreased terminal/vellus ratio), and the biopsies may resemble those of androgenetic alopecia. There is usually no inflammation (Fig. 68.19c).

Trichotillomania and tinea capitis are the most important differential diagnoses. The differentiation of diffuse alopecia areata from TE can be challenging. Lupus and secondary syphilis may also be considered in the differential diagnosis of patchy alopecia areata.

Therapeutic Approach There is still no approved drug in the United States for the treatment of alopecia areata [59] although many are used, for example contact sensitizers, intralesional or topical steroids, systemic steroids, and immunosuppressors. Considering the possibility of spontaneous remission, especially for those in the early stages of the disease, the option of not being treated therapeutically may be an alternative way of dealing with this condition [58].

Fig. 68.19 (**a**) Alopecia areata, acute stage: dense lymphocytic infiltrate affecting the follicular matrix of an anagen follicle. A telogen follicle is noted in the vicinity (Courtesy of Dr. Maria Miteva, Miami, USA). (**b**) Alopecia areata, subacute stage: note the increased number of telogen follicles in this horizontal section (telogen count of 50%) (Courtesy of Dr. Maria Miteva, Miami, USA). (**c**) Alopecia areata, chronic stage: there are only four vellus follicles and no terminal follicles in this biopsy. Note the fibrous streamers in the dermis (Courtesy of Dr. Maria Miteva, Miami, USA)
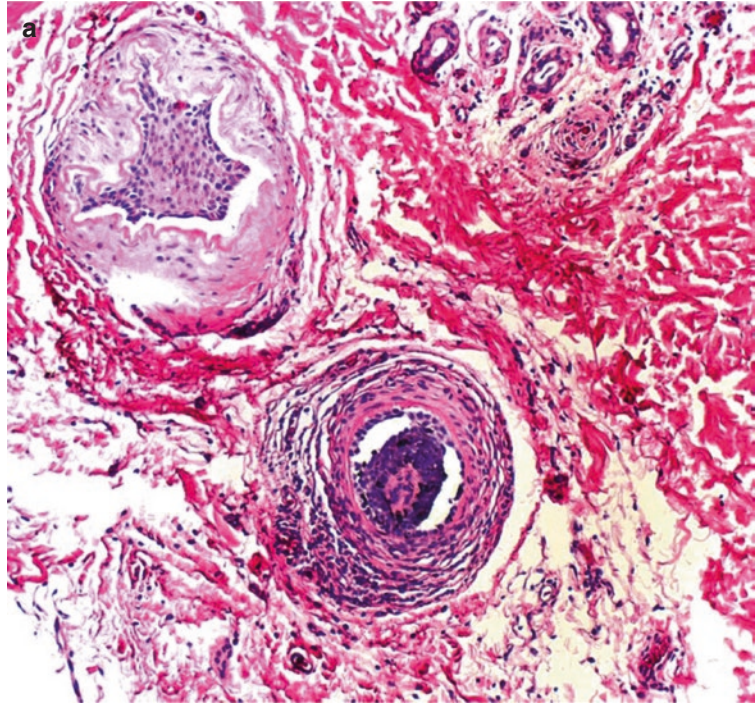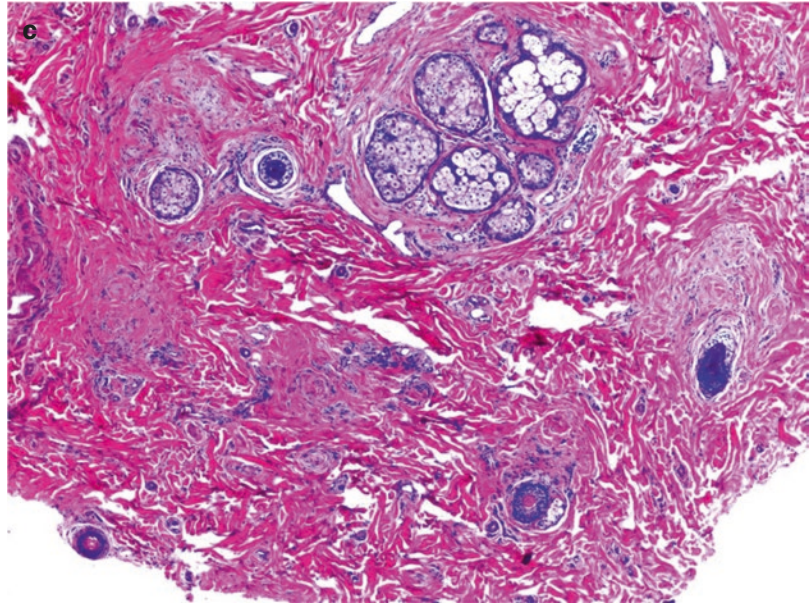
Androgenetic Alopecia or Female and Male Pattern Hair Loss

Introduction and Etiopathogenesis Androgenetic alopecia (AGA) affects both genders and is an androgen-related condition that develops in genetically predisposed individuals [65]. There is a progressive reduction in the average duration of the anagen phase (the growth period) at each hair cycle and, for this reason, the hair follicles become progressively smaller and the hair shorter and thinner. There is also an increase of the physiologic kenogen interval (period between the loss of the hair in telogen and its replacement with new hair), causing empty follicles [66, 67]. The pathogenesis of this disease is polygenic, and in men is particularly related to dihydrotestosterone (DHT). The concentration of DHT levels and 5α-reductase activity are increased on balding areas of the scalp in these patients. In women, the term female pattern hair loss (FPHL) is the preferred appellation, because not all women with this condition present a clear genetic and androgenic trait [68]. Signs of hyperandrogenism (hirsutism, irregular periods) or hyperandrogenemia occur in a subset of women with FPHL, but most women with FPHL have neither [69].

Clinical Features and Diagnosis In the majority of men, balding is patterned, the two major components being frontotemporal recession and loss of hair over the vertex. Hamilton classified male AGA into several stages, and his classification was subsequently revised by Norwood. A small proportion of men show a diffuse pattern of hair loss, similar to FPHL [70]. In FPHL, terminal, thick hair follicles, mainly localized in the frontal parietal scalp and vertex, become thinner, shorter, and less pigmented, and appear very similar to vellus hairs [68].

Dermoscopically male and female AGA share similar trichoscopic features, including hair shaft thickness heterogeneity, thin hairs, yellow dots, peripilar sign (brown perifollicular discoloration), an increased proportion of vellus hairs, and a large number of follicular units with one hair shaft. Honeycomb pigmentation can be observed, which is due to increased sun exposure of an unprotected scalp [71]. In trichoscopy of AGA the abnormalities are more pronounced in the frontal than in the occipital area, as seen on Figs. 68.20 and 68.21.

Pathologically, the main finding is the presence of follicular miniaturization. There is a decreased terminal/vellus ratio of less than 2:1.

Fig. 68.20 Androgenetic alopecia: hair shaft thickness heterogeneity, with multiple vellus hairs, increased proportion of follicular units with one hair, and honeycomb hyperpigmentation (Courtesy of Dr. Patricia Damasco, Brasilia, Brazil)
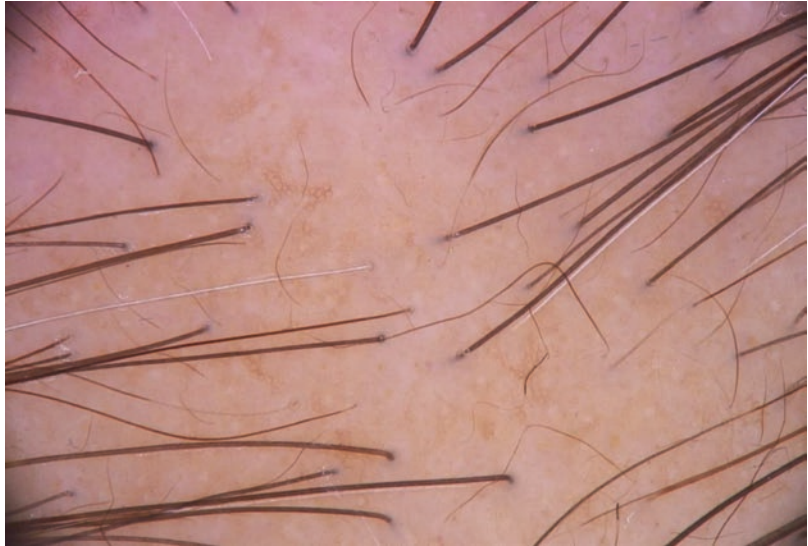
Fig. 68.21 Androgenetic alopecia: yellow dots, thin wavy hair (Courtesy of Dr. Patricia Damasco, Brasilia, Brazil)

The telogen count may be slightly increased to about 19–20% (Fig. 68.22).

Differential diagnosis includes alopecia areata incognita, frontal fibrosing alopecia with fronto-temporal onset, fibrosing alopecia in a pattern distribution, and psychogenic alopecia; TE can resemble AGA.

Therapeutic Approach Topical minoxidil and finasteride (5α-reductase type II inhibitor) are the only treatments approved by the US Food and Drug Administration (FDA) for male androgenetic alopecia. In women, the only FDA-approved drug is topical minoxidil [68]. Oral antiandrogens and other therapeutic options can be used as adjuvants to prevent the progression of hair loss and stimulate partial regrowth of hair. Combining medications with different mechanisms of action enhances the efficacy. Surgical treatment of follicular unit hair transplantation is an option in cases that have failed medical treatment.

Fig. 68.22 Androgenetic alopecia: horizontal section at the isthmus/infundibulum level. There are 8 terminal follicles and 15 the vellus follicles (terminal/vellus ratio 0.6:1) (Courtesy of Dr. Maria Miteva, Miami, USA)
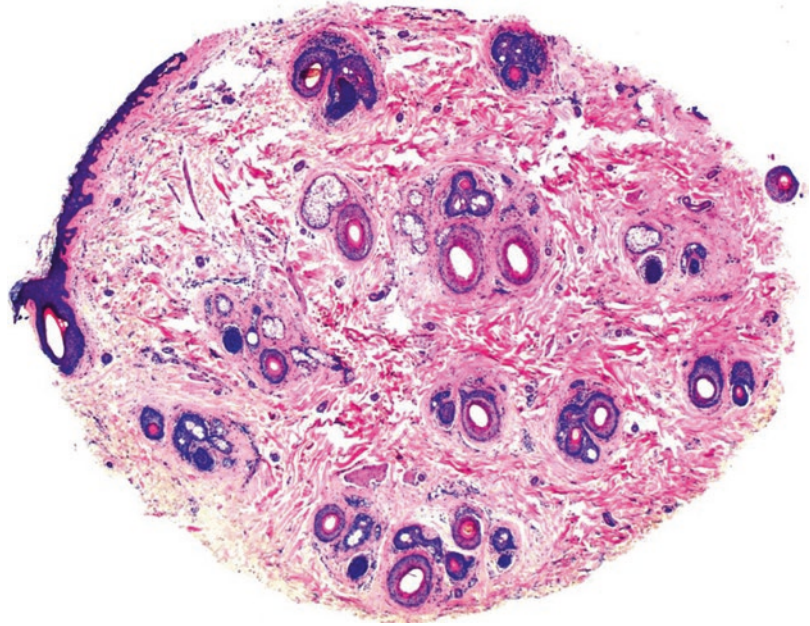
Trichotillomania

Introduction and Etiopathogenesis Trichotillo mania (TTM) is a psychiatric disorder characterized by an irresistible urge to pull out one's hair [72]. The condition most affects children from 9 to 13 years, although adult onset may be secondary to underlying psychiatric disturbances and has a long-lasting course [73]. Usually hair pulling is preceded by mounting tension and consequently brings relief or gratification [74]. Patients frequently experience co-occurring anxiety disorders, depressive disorders, and other body-focused repetitive behaviors [75].

Clinical Features and Diagnosis Patients present with single or multiple, usually irregular, hairless areas, predominantly in the parietal and vertex regions of the scalp. However, any area of the body can be affected.

Pathologically the biopsy of trichotillomania shows increased telogen count of up to 70%. The majority are catagen follicles, which may be arranged in groups. The differential diagnosis with alopecia areata, particularly with the subacute stage, can be difficult but the presence of trichomalacia (fragmented or distorted hair

shafts in the follicular canal) and pigmented casts can indicate the diagnosis of trichotillomania [76]. The pigmented casts are black clumps of melanin usually with a weird shape, and are encountered at different follicular levels (Fig. 68.23).

Trichoscopy shows decreased hair density, broken hairs at different lengths, short hairs with trichoptilosis, irregular coiled hairs, flame hairs, V-sign, hair powder, upright regrowing hairs, and black dots (Fig. 68.24a–c) [77, 78].

Differential diagnosis includes alopecia areata, androgenetic alopecia, and tinea capitis. Sometimes alopecia areata and trichotillomania can coexist in the same patient, making trichoscopic differential diagnosis even more challenging [77].

Therapeutic Approach Treatment options include specialized age-adapted behavioral therapy, such as habit reversal training, and psychiatric medications [75]. More recently, *N*-acetylcysteine (NAC) has been evaluated in the treatment of TTM. Although offering promise for some individuals, the small number of randomized controlled trials limits inferences about NAC's efficacy for TTM [75, 79].
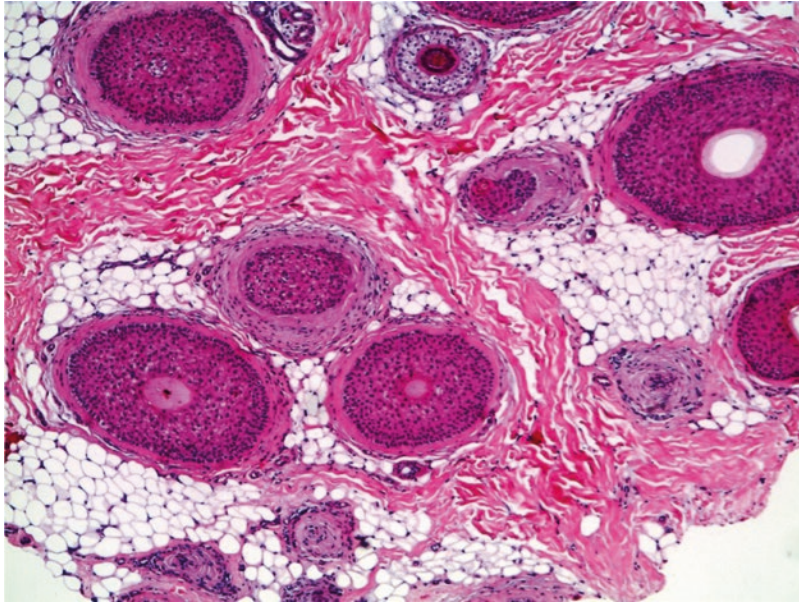
Fig. 68.23 Trichotillomania: increased number of telogen follicles. Note the black pigmented casts with trichomalacia in the follicular canals of two affected follicles (Courtesy of Dr. Maria Miteva, Miami, USA)
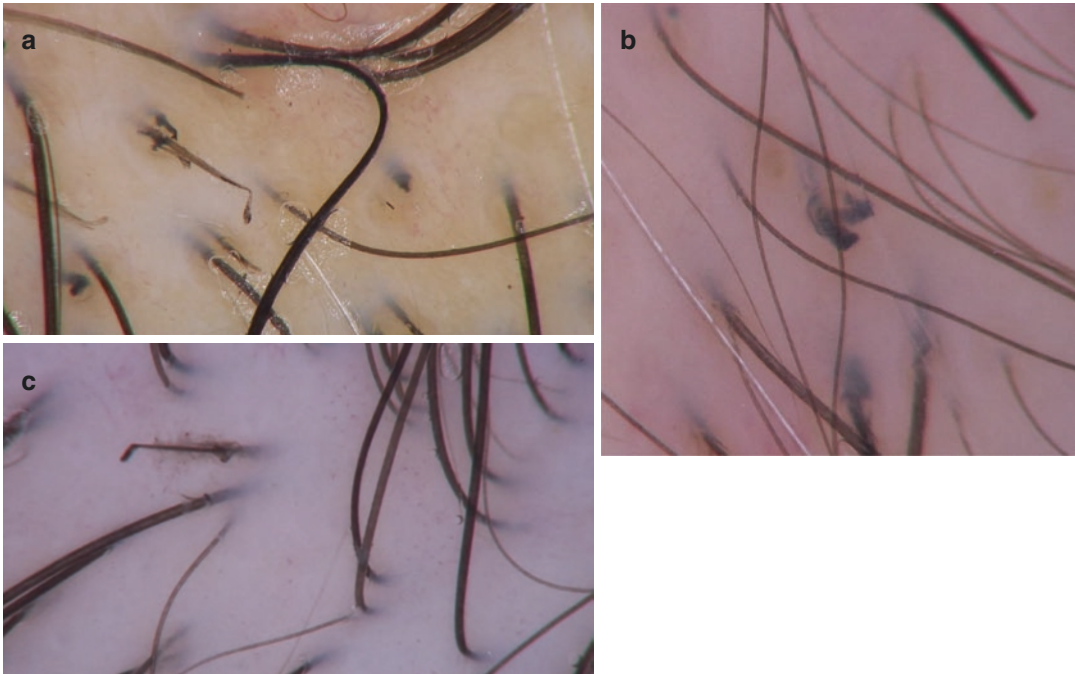
Fig. 68.24 (**a**) Trichotillomania: coiled hairs, flame hair, and broken hairs (Courtesy of Dr. Patricia Damasco, Brasilia, Brazil). (**b**) Trichotillomania: V-sign is created when two or more hairs emerging from one follicular unit are pulled simultaneously and break at the same length (Courtesy of Dr. Patricia Damasco, Brasilia, Brazil). (**c**) Trichotillomania: hair powder in trichotillomania (Courtesy of Dr. Patricia Damasco, Brasilia, Brazil)

Primary Cicatricial Alopecia

Scarring and cicatricial alopecia are synonymous, and mean that hair follicles are replaced by connective tissue. This event occurs because stem cells of bulges are damaged. Some scarring alopecia has a biphasic pattern; the early phase of injury is nonscarring alopecia, and with the time it confers permanent damage, as seen in traction alopecia and discoid lupus erythematosus alopecia. The opposite occurs, for example, in nonscarring alopecia such as androgenetic alopecia, which in time can become cicatricial alopecia.

It is important to understand that in primary alopecia the focus of damage is the hair follicles. However, there are secondary scarring alopecias, such as radiation dermatitis, morphea, and chronic infections, whereby the hair damage is secondarily affected by the damage to surrounding tissue.

Lichen Planopilaris

Introduction and Etiopathogenesis Lichen planopilaris (LPP) is an inflammatory lymphocyte cicatricial alopecia, and is considered the most frequent cause of adult primary scarring alopecia [80]. There are three variants of LPP: classic LPP, frontal fibrosing alopecia (FFA), and Graham-Little-Piccardi-Lasseur syndrome (GLPLS) [80–82]. Some authors consider fibrosing alopecia in a pattern distribution (FAPD) a fourth variant of the disease [80–82]. Women between the ages of 40 and 60 years are more frequently affected [81]. Classic LPP can be associated with nonscalp lichen planus in 50% of cases during the course of disease [83]. The cause of LPP remains unknown. The antigenic trigger remains unidentified, and the inflammatory infiltration occurs around the bulge area, mediated by T lymphocytes activated by Langerhans cells [81].

Clinical Features and Diagnosis Classic LPP is the most common variant of LPP and usually involves the vertex, as seen in Fig. 68.25. However, it can occur on any part of the scalp as a solitary or multiple areas of baldness, with patches stretched centrifugally [84]. The symptoms are hair shedding, scales, scalp tenderness, or pruritus, although patients sometimes do not complain of any symptoms [84].

Dermoscopically, there are different trichoscopic features of classic LPP in active and inactive lesions. Usually active lesions show perifollicular scaling that tends to form tubular structures in hair casts (tubular hyperkeratosis), violaceous areas, and elongated linear blood vessels, as seen

Fig. 68.25 Lichen planopilaris: single patch on the vertex area (Courtesy of Dr. Giselle Martins Pinto, Porto Alegre, Brazil)
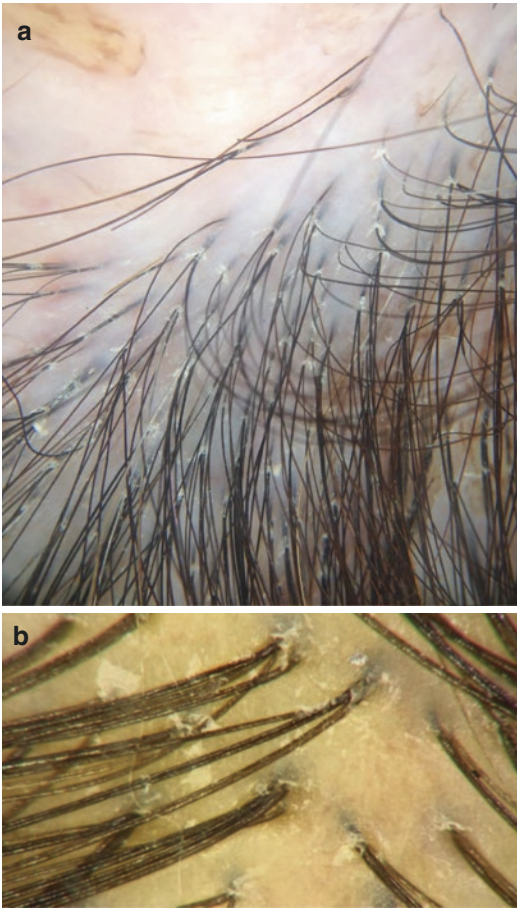
Fig. 68.26 (**a**, **b**) Dermoscopy of lichen planopilaris: cicatricial alopecia and keratosis perifollicularis, tufted hairs (Courtesy of Dr. Giselle Martins Pinto, Porto Alegre, Brazil)

on Fig. 68.26a, b [80]. In inactive lesions one observes white areas, irregular and large white dots (fibrotic white dots), milky red areas (strawberry ice cream color), and tufted hairs [80].

Pathologically, primary cicatricial alopecia is characterized by altered follicular architecture with decreased follicular density and eventual loss of the follicular units (follicular dropout) due to their replacement by scar tissue. Dermoscopy-guided biopsies and horizontal sections are helpful in detecting focal involvement [85]. The sebaceous glands are usually absent or diminished. In the early active stage, there is follicular inflammation which, depending on the type of predominant cells, can be primarily lymphocytic (primary lymphocytic cicatricial alopecia) or of mixed cell type (primary neutrophilic cicatricial alopecia). There is altered follicular architecture with areas of follicular dropout and absence of sebaceous glands (Fig. 68.27). The main pathologic finding is the presence of perifollicular lichenoid lymphocytic infiltrate, which can be encountered at the lower follicular levels but is most pronounced at the level of the isthmus. The infiltrate can invade the outer root sheath in a more interfaced pattern. There is perifollicular concentric fibrosis. In FFA there are usually more apoptotic cells in the outer root sheath (Fig. 68.28) [86].

Fig. 68.27 Lichen planopilaris: In this horizontal section at the isthmus level there are compound follicular structures ("goggles") showing perifollicular inflammation and fibrosis. Note the absence of sebaceous glands (Courtesy of Dr. Maria Miteva, Miami, USA)
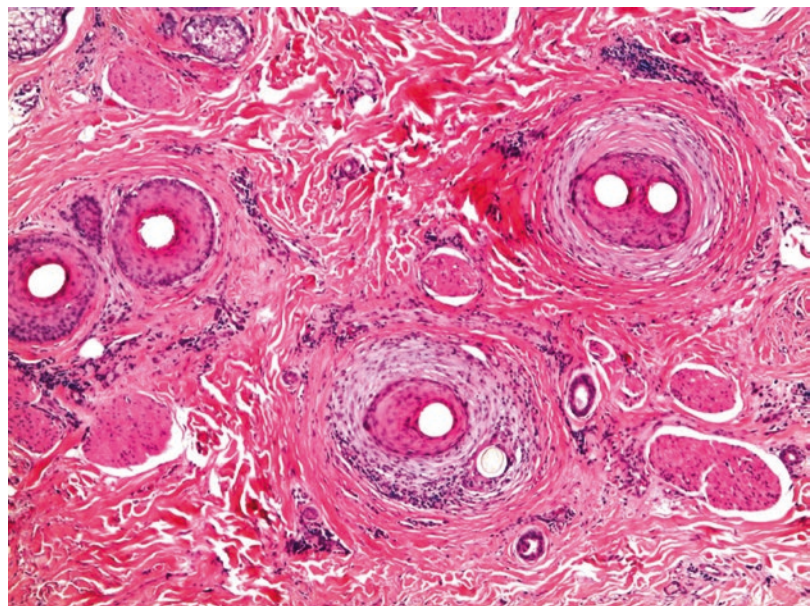
Differential diagnosis includes psoriasis, SD, folliculitis decalvans, FFA, and cicatricial pemphigoid, among others.

Therapeutic Approach Therapy is often not satisfactory [81]. Topical and intralesional corticosteroids are usually helpful. Systemic treatment can include oral corticosteroids, cyclosporine, antimalarials, mycophenolate mofetil, and thalidomide as second-line therapy. Excimer laser treatment may be attempted if any of these medications fail to control the disease [87].

Frontal Fibrosing Alopecia

Introduction and Etiopathogenesis FFA is a primary lymphocytic cicatricial alopecia that more frequently affects postmenopausal women [80]. Only 7.6% of all cases of FFA are premenopausal women and 1.9% are men [88]. FFA is considered a variant of LPP, but some authors believe FFA to be a different disease. The pathogenesis is uncertain, although an androgen effect has been speculated because of the strong association with postmenopausal status [89].

Clinical Features and Diagnosis A progressive frontotemporal symmetric band of alopecia is the most common presentation, as seen on Fig. 68.29

[89]. The skin at the recession area is smooth and shiny, contrasting with the rest of facial skin and indicating where the former hairline used to be [84]. FFA can cause mild pruritus or be asymptomatic. There is a very interesting association with eyebrow loss. In some patients the alopecia is associated with lichen planus pigmentosus of the face, and facial papules that usually show vellus follicle involvement or hyperplasia of sebaceous glands [90, 91].

Dermoscopically there is lack of follicular openings, perifollicular erythema, and scaling on a homogeneous ivory-colored background [80]. The important clue for dermoscopy is the loss of hair vellus on the hairline, as seen on Fig. 68.30.

Pathologically, FFA and LPP are the same; see the description above of LPP.

In the differential diagnosis it is important to bear in mind that some diseases can be clinically similar to FFA, such as ophiasic alopecia areata, lupus erythematosus, traction alopecia and androgenetic alopecia.

Therapeutic Approach Usually FFA is treated as classic LPP, although finasteride has been reported to halt the progression of this disease [92]. Hair transplants can be proposed after no disease improvement for at least 1–2 years [80].

Fig. 68.28 Frontal fibrosing alopecia: follicular lichenoid and interface lymphocytic infiltrate and fibrosis. Note the apoptotic cells in the outer root sheath (Courtesy of Dr. Maria Miteva, Miami, USA)
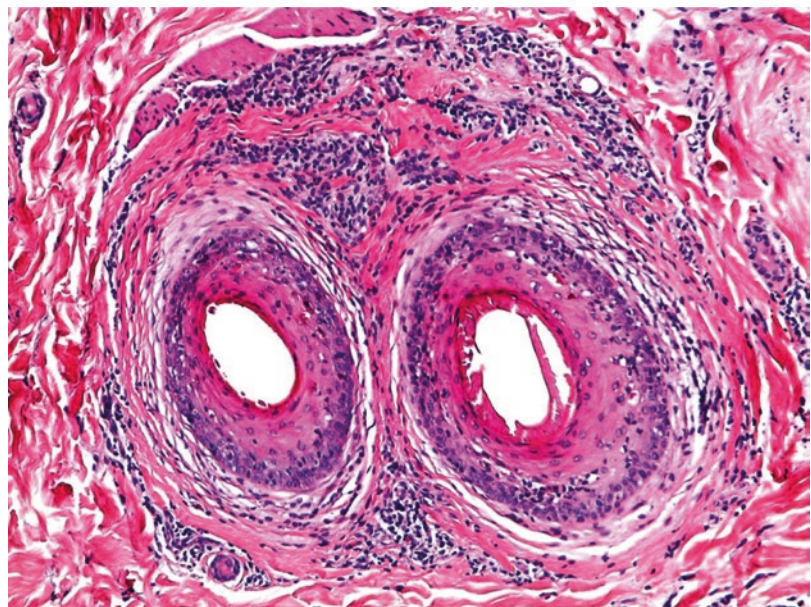
Fig. 68.29 FFA: progressive frontotemporal symmetric band of alopecia (Courtesy of Dr. Giselle Martins Pinto, Porto Alegre, Brazil)

Fig. 68.30 FFA: lack of follicular openings, erythema and scaling, and loss of hair vellus on hair (Courtesy of Dr. Giselle Martins Pinto, Porto Alegre, Brazil)

Graham-Little-Piccardi-Lasseur Syndrome

Introduction and Etiopathogenesis GLPLS is a rare disease, affecting women between 30 and 60 years of age. Some authors consider this disease a variant of LPP [80, 93].

Clinical Features and Diagnosis The triad of progressive scarring scalp alopecia, nonscarring loss of pubic and axillary hair, and disseminated follicular papules with spinous scales is characteristic [84]. The scalp disease clinically and histopathologically resembles classic LPP.

Trichoscopy of the scalp is similar to that of classic LPP, although the pubic and axillary areas do not show the dermoscopy signs of LPP, merely thin hairs [80].

Pathologically, GLPLS is the same as LPP.

The main differential diagnosis is classic LPP, although lupus erythematosus must be considered.

Therapeutic Approach Treatment is similar to LPP treatment.

Fibrosing Alopecia in a Pattern Distribution

Introduction and Etiopathogenesis FAPD was for the first time described in 2000. This new form of cicatricial alopecia is not yet well recognized as a variant of LPP, a variant of androgenetic alopecia, or an authentic entity [81].

Clinical Features and Diagnosis Clinically the patients present a pattern similar to that of androgenetic alopecia. The hair loss is limited to the area of androgenetic alopecia.

Dermoscopically, perifollicular erythema and hyperkeratosis is universally seen.

Pathologically, FAPD is consistent with features of LPP with follicular miniaturization.

The differential diagnosis includes AGA, LPP; sometimes AGA and LPP can coexist in the same patient.

Therapeutic Approach Some authors have reported improvement with agents such as finasteride and minoxidil; however, many clinicians prefer drugs used for classic LPP, such as topical or systemic corticosteroids.

Discoid Lupus Erythematosus Alopecia

Introduction and Etiopathogenesis Discoid lupus erythematosus (DLE) alopecia is seen more frequently in young women. Usually it is considered a local disease, as less than 5% of DLE patients have systemic disease [84]. DLE alopecia is classified as primary lymphocytic cicatricial alopecia; however at the beginning of the disease, because the target is not the hair follicles, the alopecia can be reversed with the appropriate treatment. The pathogenesis of DLE involves interaction between genetic, environmental, and host factors [84].

Clinical Features and Diagnosis DLE alopecia begins as a well-demarcated round or oval purplish macule or papule, and enlarges into an alopecic patch with follicular plugging, erythema, and adherent scaling [80]. Commonly it is seen in the vertex, as a single or multiple patches [94]. Symptoms include pruritus, scalp tenderness, hair shedding, burning, and, less commonly, pain [80]. Long-standing DLE alopecia has fibrotic atrophic and white plaques with lack of hair openings.

Dermoscopically, in active lesions one sees thick arborizing vessels, large yellow dots that correspond to follicular keratotic plugs, and fine interfollicular scaling, as seen in Fig. 68.31 [81]. Red dots indicate dilated infundibula surrounded by dilated vessels and extravasated erythrocytes, and represent a good prognosis and chance of hair regrowth [95]. The blue-gray dots seen on dark or sun-exposed skin correlate with pigment incontinence secondary to interface dermatitis [96]. In long-standing inactive lesions one sees loss of follicular openings, pink areas, white areas, arborizing vessels, and yellow dots containing thin spider vessels in prefibrotic lesions [80].

Pathologically, at the level of the bulb in the subcutaneous fat there is perivascular and periadnexal (perieccrine and perifollicular) infiltrate of

Fig. 68.31 DLE: in active lesions there are thick arborizing vessels, large yellow dots (follicular keratotic plugs), and fine interfollicular scaling (Courtesy of Dr. Giselle Martins Pinto, Porto Alegre, Brazil)

lymphocytes and plasmacytoid cells, which can aggregate in germinal center-like collections (Fig. 68.32a). The infiltrate also affects the upper follicular levels in an interface follicular pattern.

The sebaceous glands are absent, but there is no prominent perifollicular fibrosis as seen in lichen planopilaris. There is interface dermatitis along the dermoepidermal junction with pigment

incontinence and thickened basement membrane. The follicular infundibula are plugged by keratin (Fig. 68.32b). The dermis and subdermis appear pale and loose because of deposition of mucin.

The most frequent differential diagnosis of DLE alopecia is LPP. However, sometimes one excludes SD, psoriasis, cicatricial pemphigoid, and basal cell carcinoma.

Therapeutic Approach Photoprotection should be advised, as DLE alopecia worsens in upon sun exposure. Topical treatments include potent topical steroids, calcineurin inhibitors, retinoids, and imiquimod, with mixed outcomes. Intralesional steroids are indicated in small areas of alopecia, although there is always a risk of scarring alopecia after the treatment, with depressions on the skin surface. Systemic treatment include antimalarial drugs, systemic steroids, and thalidomide, similar to the treatment of cutaneous lupus erythematosus.

Folliculitis Decalvans

Introduction and Etiopathogenesis Folliculitis decalvans (FD) is a primary neutrophilic scarring alopecia. It is a disease seen in male patients, more commonly in African American men [83]. The pathogenesis of FD is poorly understood; some authors believe that superantigens and an exaggerated immune response might play a role.

Clinical Features and Diagnosis Recurrent follicular pustules involve the vertex and occipital area of the scalp. Patches of alopecia are seen in one or more area. Patients complain of pain, itching, and burning sensation, and the lesions usually are malodorous because of discharge of material from the pustules and hemorrhagic crust lesions. Clinically there are tufts comprising multiple hairs (6–20+ hairs) emerging from one single dilated follicular orifice.

At dermoscopy, active disease shows tufted hairs with more than five hairs in one follicular unit, yellow follicular pustules, yellowish tubular scaling with collar formation, yellow discharge, epidermal hyperplasia and vessels with elongated loops, and concentric perifollicular arrangement, as seen in Fig. 68.33 [80]. Starburst sign consists of yellowish scales and perifollicular epidermal hyperplasia that may be in a starburst pattern [80]. In late-stage or inactive disease, only cicatricial alopecia as white and milky red areas without follicular openings and epidermal hyperplasia are apparent.

Pathologically, in FD there is dense perifollicular but also interfollicular infiltrate of mixed cell origin (lymphocytes, histiocytes, neutrophils, and plasma cells). The main finding is the presence of compound follicular structures (tufts of hairs on clinical examination) arising from the fusion of the outer root sheaths of variable number of follicles but usually of more than 2 (Fig. 68.14). There is perifollicular fibrosis and absence of sebaceous glands. In advanced stages, there is prominent follicular dropout (Fig. 68.34).

Fig. 68.33 Folliculitis decalvans: dermoscopy shows tufted hairs with more than five hairs in one follicular unit and epidermal hyperplasia (Courtesy of Dr. Giselle Martins Pinto, Porto Alegre, Brazil)

Fig. 68.34 Folliculitis decalvans: compound follicular structures (six packs in this case). Note the dense interfollicular inflammation and the perifollicular fibrosis. The sebaceous glands are absent (Courtesy of Dr. Maria Miteva, Miami, USA)
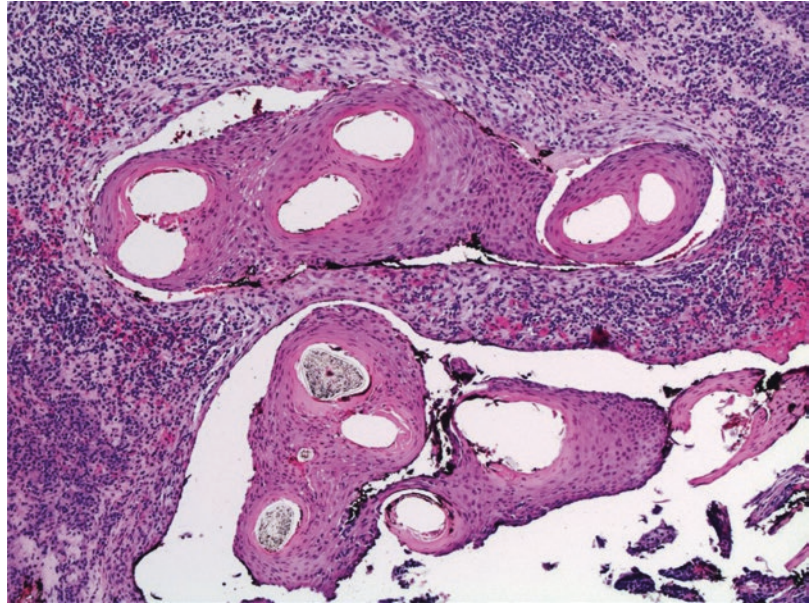
The main differential diagnosis is with disease that causes tufted hairs, such as LPP. Rarely other diseases has tufted hairs, e.g., DLE alopecia, central centrifugal cicatricial alopecia, and dissecting cellulitis.

Therapeutic Approach Various case reports indicate that the use of oral antibiotics in combination may have success as an alternative therapy, such as oral rifampicin and clindamycin, doxycycline, ciprofloxacin, or clarithromycin [97].

Dissecting Cellulite

Introduction and Etiopathogenesis Dissecting cellulite (DC) of the scalp, dissecting folliculites, and perifolliculites capitis abscedens et suffodiens are synonyms, and occur most commonly in young adult men with dark skin phototypes [80]. DC can occur as isolated on the scalp or be part of the follicular occlusion tetrad: DC, pilonidal cyst, hidradenitis suppurativa, and acne conglobata. The pathogenesis of this disease is unknown, although some authors believe there exists a correlation between follicular hyperkeratosis and superinfection.

Clinical Features and Diagnosis DC is a chronic, relapsing, and progressive cicatricial alopecia [80]. Usually the patients complain of perifollicular pustules or firm scalp nodules on the vertex or occiput area. These nodules are firm or fluctuant and can discharge a purulent material. Frequently the material is sterile, but sometimes secondary bacterial infections may occur.

On dermoscopy, active disease shows yellow structureless areas, yellow 3D dots (three-dimensional structures) with or without dystrophic hair shafts, black dots, pinpoint-like vessels with a whitish halo, and cutaneous clefts with emerging hairs and hair tufts [80]. End-stage lesions show white areas with lack of follicular openings.

Pathologically, biopsies from early disease show dense and diffuse mixed cell infiltrate occupying the lower part of the dermis and the subdermis. The infiltrate also contains giant cells. There is edema and red blood cell extravasation. The majority of the follicles are in telogen and the sebaceous glands may still be preserved at that stage (Fig. 68.35). It is distinguished from inflammatory tinea capitis by the fact that infiltrate is mostly in the lower portion of the specimen in DCS.

Fig. 68.35 Dissection cellulitis of the scalp, early disease: the follicular architecture is altered by the presence of dense mixed cell infiltrate with edema and red blood cell extravasation. The telogen count is increased (Courtesy of Dr. Maria Miteva, Miami, USA)
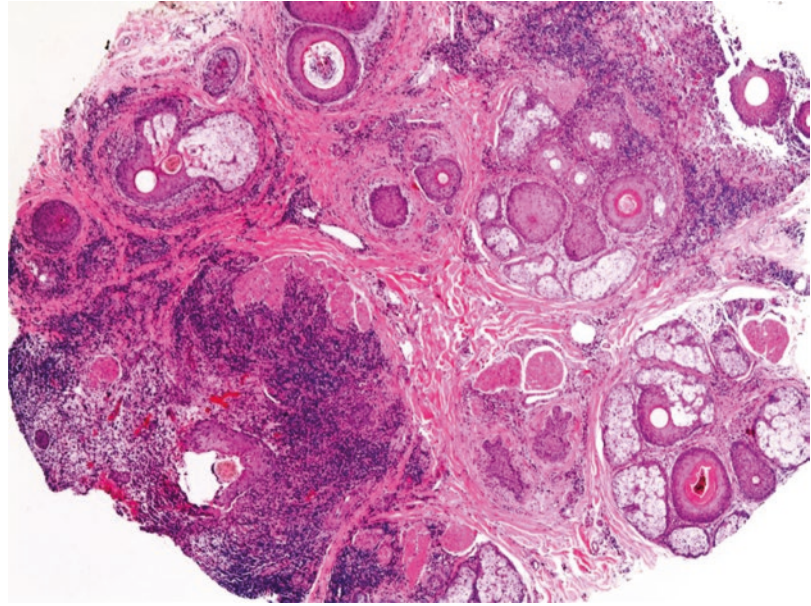
The differential diagnosis of FD includes alopecia mucinosa, tinea capitis, and acne keloidalis nuchae.

Therapeutic Approach The literature has reported the use of isotretinoin as an effective therapy for this disease, although relapses are common. Alternative treatments include intralesional steroids, oral antibiotics, and surgery for specific cases.

Central Centrifugal Cicatricial Alopecia

Introduction and Etiopathogenesis Central centrifugal cicatricial alopecia (CCCA), follicular degeneration syndrome, and hot comb alopecia are synonyms. This disease is the most common scarring alopecia in African American women [98]. Almost all black women of African descent with CCCA have used chemical hair relaxers. However, after discontinuing the use of these chemical treatments the disease can progress. The current hypothesis is that the anatomic abnormality is due to premature desquamation of the inner root sheath [98].

Clinical Features and Diagnosis This disease is a chronic, progressive cicatricial alopecia usually on the vertex or crown. CCCA has a symmetric appearance, with the surrounding zone showing activity similar to that of most common scarring alopecia. Most of the patients have no symptoms, or mild pruritus or tenderness of the involved area. Bacterial superinfections can occur, and in such cases pustules and crusting is described.

The trichoscopic features of CCCA include loss of follicular openings.

Pathologically, there is altered follicular architecture with areas of follicular dropout. The follicular density is decreased and in most cases there is diminished terminal/vellus ratio of about 2:1. The affected follicles show perifollicular concentric fibrosis and, rarely, mild perifollicular lichenoid lymphocytic infiltrate. Often they form compound follicular structures ("goggles") which correspond to pairs of follicles fused by their outer root sheaths and surrounded by concentric fibrosis. The sebaceous glands are focally preserved and often surround vellus follicles [99]. Naked hair shafts are found in the dermis. Premature desquamation of the inner root sheath supports the diagnosis (Fig. 68.36).

Fig. 68.36 CCCA: compound follicular structures ("goggles") showing perifollicular fibrosis but only mild inflammation. The sebaceous glands are focally preserved (Courtesy of Dr. Maria Miteva, Miami, USA)
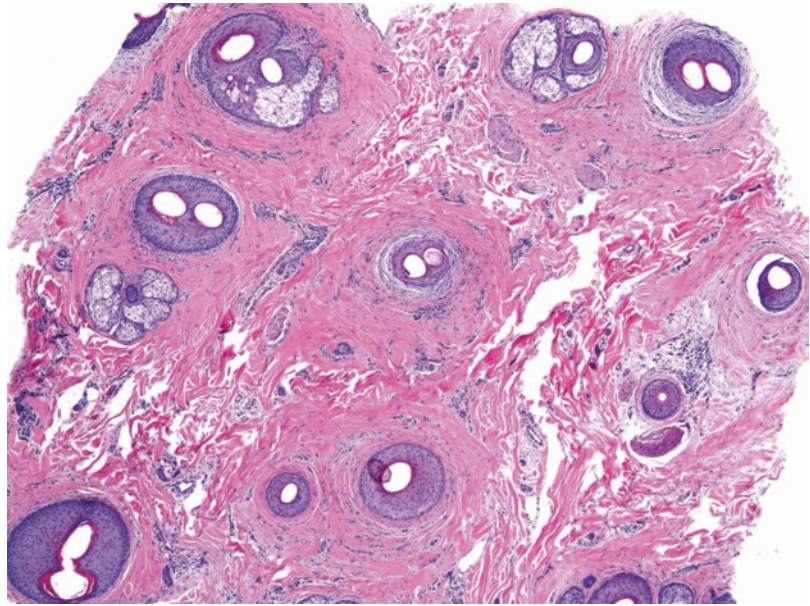
In the differential diagnosis, usually CCCA can be confused with AGA, FD, or LPP.

Therapeutic Approach A combination of oral antibiotics, such as doxycycline or tetracycline, with topical steroids is the most common treatment reported in the literature [98].

Traction Alopecia

Introduction and Etiopathogenesis Traction alopecia (TA) is most commonly caused by hairstyling procedures, and African American women are frequently affected. The most common procedures include ponytails, tight buns, weaves, dreadlocks, cornrows, clips, hair extensions, tight braids, hair relaxers, and stretching of scalp hair.

Clinical Features and Diagnosis TA is a biphasic form of hair loss. In the early phase the alopecia is reversible, and if the traction stops hair regrowth can occur. However, if the traction is maintained for years, the hair loss becomes a permanent area of alopecia. Persistent, bitemporal, or frontal hair loss is the most common pattern, as seen in Fig. 68.37.

Two phases are observed on dermoscopy. First one can observe perifollicular erythema, hair

Fig. 68.37 Traction alopecia: linear hair loss and use of hair extensions (Courtesy of Dr. Giselle Martins, Porto Alegre, Brazil)

thinning, focal decrease of hair density, broken hairs, and tulip hairs [80]. Hair casts are characterized by white keratin cylinders around the hair shaft. With progressive traction, perifollicular scarring and cicatricial alopecia ensue.

Pathologically, early cases may show overall preserved follicular architecture with only focal

Fig. 68.38 Traction alopecia: at the level of the isthmus the follicular architecture is preserved overall with only one area of follicular dropout. The sebaceous glands are intact. Only one vellus follicle is present (Courtesy of Dr. Maria Miteva, Miami, USA)
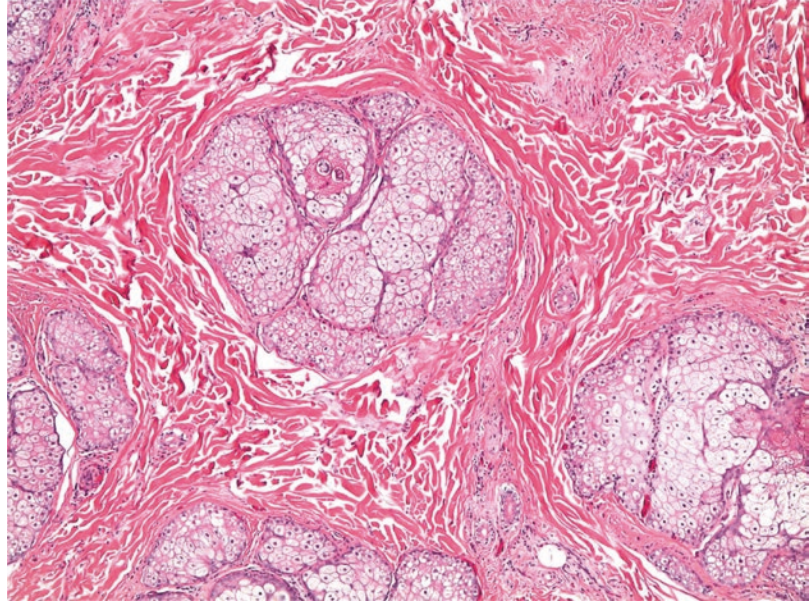
areas of follicular dropout, with no follicular inflammation or fibrosis and intact sebaceous glands. In advanced cases, follicular dropout may dominate. The terminal/vellus ratio is significantly decreased, with vellus follicles outnumbering the terminal follicles (Fig. 68.38).

The differential diagnosis includes TTM, FFA, and LPP.

Therapeutic Approach The most important treatment approach is to stop the traction.

Glossary

Effluvium Shedding of hair.

Endothrix infection Dermatophyte infections of the hair that invade the hair shaft and internalize into the hair cell. The hair shaft is filled with fungal branches (hyphae) and spores (arthroconidia). Endothrix infections do not fluoresce with Woods light.

Pityriasis amiantacea A scalp condition that causes scaling, and can occur in patches anywhere on the scalp. It is an eczematous condition of the scalp resulting in hair loss, whereby thick adherent scale infiltrates and surrounds the base of a group of scalp hairs.

Psoriasiform acanthosis The presence of evenly elongated, thin rete ridges with equally long dermal papillae.

Trichotillomania A disorder that involves recurrent, irresistible urges to pull out hair from the scalp, eyebrows, or other areas of the body, despite trying to stop. Hair pulling from the scalp often leaves patchy bald spots.

Trichoscopy Hair and scalp dermoscopy. May be performed with a handheld dermoscope. This makes it a modern, noninvasive technique.

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Nail Diseases

69

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Key Points Summary
- Onychomycosis is one of the most common infections of the nail apparatus via fungi and accounts for more than 50% of nail diseases. In turn, periungual warts are infections caused by the human papilloma virus
- Among the more important inflammatory skin diseases affecting the nails are lichen planus and psoriasis
- Lichen planus is a chronic, inflammatory, autoimmune disease that leads to destruction of basal keratinocytes, causing anonychia and permanent atrophy. Early diagnosis is essential and therapy should start immediately
- Psoriasis is a chronic inflammatory skin disease that can also affect the nails. It is thought that 80–90% of patients with psoriasis will at some point present with nail involvement. Fingernails are more commonly affected than toenails
- Among the nail dyschromias melanonychia, the brown to black color of the nail plate, which requires the important differential diagnoses such as melanoma, is noteworthy
- Ingrown toenails result from an imbalance between nail plate width, nail bed, and lateral nail fold hypertrophy. There are four types of ingrown nails: ingrowing toenail in infancy, lateral and distal nail fold hypertrophy, pincer nails, and juvenile ingrown toenail
- Paronychia is a multifactorial inflammatory disorder affecting proximal and lateral nail folds

This chapter is an approach of clinical interest onychopathies. All photos are of Dr. Renan Minotto's collection.

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Onychomycosis

Introduction

Onychomycosis is one of the most common fungi-related infections of the nail apparatus and accounts for more than 50% of nail diseases. Several studies have shown its relevance, which can be explained

by factors such as associations with other diseases, increase in life expectancy within the population, and increasing attention to nail conditions by clinicians and patients [1]. Many species of nail fungi exist, and under conditions of moisture and heat these fungi grow quickly. Three groups of fungi cause this disease: dermatophytes, yeasts, and nondermatophyte molds [1, 2].

In certain populations (e.g., soldiers, swimmers, students, runners, sports participants), the prevalence of onychomycosis can be much higher. Several factors have resulted in an increased prevalence of onychomycosis, including wearing of shoes, particularly tight shoes; the use of damp spaces such as locker rooms and gymnasiums; and frequent nail traumas [3].

Concepts

Fungal infection of the nail is considered cosmopolitan and recalcitrant dermatosis. It should not be viewed as a mere aesthetic problem. This condition is known to require prolonged treatment with disappointing results and should be regarded as an important health issue, indicating that it is often associated with physical and psychological distress. It may interfere with the patient's quality of life; therefore, it must be treated seriously and effectively [3, 4].

Fingernails and toenails consist of a protein called keratin, which may provide substrates for the metabolism of fungi and help them to survive, leading to onychomycosis, which is highly prevalent in halluces. Some cases may be difficult to manage, especially in cases of nondermatophytic onychomycosis, even with the recent advances in antifungal drugs. Predisposing factors for onychomycosis include poor peripheral circulation, diabetes, repeated nail trauma, low immune resistance, occupation, inactivity, heat, and humidity [1–4].

Clinical Presentation

Diagnosis of fungal infection of the nails may be difficult since other diseases may clinically mimic onychomycosis. These include psoriasis

and difficulties in identifying the etiologic agent of onychomycosis, and will certainly require different treatments [1, 5].

Four types of onychomycosis are recognized [1, 7]. (1) Distal subungual onychomycosis is the most common form of onychomycosis, characterized by invasion of the nail bed and underside of the nail plate beginning at the hyponychium. It migrates proximally through the underlying nail matrix. (2) White superficial onychomycosis occurs when certain fungi invade directly the superficial layers of the nail plate. It can be favored by previous traumas and occurs primarily in the toenails. (3) Proximal subungual onychomycosis is a relatively uncommon subtype and occurs when organisms invade the nail unit via the proximal nail fold through the cuticle area, penetrate the newly formed nail plate, and migrate distally. Some cases have been reported in human immunodeficiency virus patients. (4) Total dystrophic onychomycosis is used to describe end-stage nail disease caused by dermatophytes, nondermatophytes, or *Candida* sp. The entire nail unit becomes thick and dystrophic.

Nail alterations found in onychomycosis can be seen in other entities, and most of these lesions include onycholysis, subungual hyperkeratosis, color change such as leukonychia and melanonychia, and dystrophies, among others (Figs. 69.1, 69.2, and 69.3). The differential diagnosis should include psoriasis, lichen planus, and traumatic onychopathies [3, 6].

Onycholysis is the separation of the nail from the nail bed. This separation of the nail plate begins at the proximal nail and extends to the free edge, which is seen most often in nail psoriasis. Subungual hyperkeratosis occurs as a result of

Fig. 69.1 Onychomycosis with irregular spiculated striations
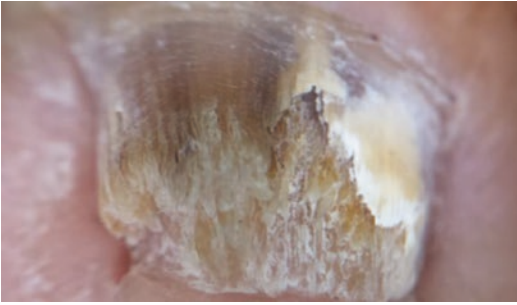
Fig. 69.2 Dermoscopy showing thickly hyperkeratosed nail plate in onychomycosis with ruin aspect

Fig. 69.3 Onycholysis and yellowish appearance of the nail plate

epithelial hyperplasia of the subungual tissues from repeated trauma and exudative skin diseases and may occur with any chronic inflammatory condition (bacterial, viral, and fungal infections) involving this area [1, 2].

Chromonychia refers to an abnormality in color of the substance or the surface of the nail plate or subungual tissues. Nail infection may well appear greenish, black, brown, or various other shades. Pseudoleukonychia caused by fungi is common [5, 6]. The presence of striated melanonychia longitudinal caused by trauma, medications, nevus, melanoma, and fungal and bacterial infection deserves attention. The lesion should be removed for biopsy in the case of suspicion of other diseases, especially melanoma. Partial ungual dystrophies are characterized by fragile, brittle nails with longitudinal or transverse cracks, and even full change of the nail plate. The small changes observed in nails may be age-related, caused by excessive exposure to detergents, nail polish removers, and the use other substances that

can dry out nails [3, 7]. Care should be taken to avoid trauma and the use of detergents, acetone, and chemicals, and to give preference to nail moisturizers that can improve the appearance of the nails. Total ungual dystrophies are commonly associated with other diseases and/or infections.

The most important differential diagnosis should include onychomycosis and psoriasis, which present symptoms such as pitting, nail discoloration, onycholysis, subungual hyperkeratosis, and even total ungual dystrophy in some cases. These two nail abnormalities can be present simultaneously. Lichen planus of nails are associated with nail changes including longitudinal grooming, nail pterygium, nail loss, and subungual hyperkeratosis. Traumatic lesions commonly show onycholysis, leukonychia, bleeding, and pigmentation changes [2, 7].

Diagnosis

Accurate diagnosis requires direct microscopy, fungal culture, and histologic examination when necessary. Direct microscopy of sampled material is necessary to definitively identify whether it is typical of dermatophyte fungi. These structures are then evaluated for morphology and coloration to help determine the clinical laboratory procedure [1, 5]. Filamentous hyaline hyphal elements characteristic of dermatophytes can be observed; the presence of pseudohyphae or tortuous hyphae, irregular, with or without conidia, can reveal nondermatophyte mycelial fungi, which makes it difficult to identify using only direct examination. In turn, the observation of the accumulation oval yeast cell forms with nonpigmented pseudofilaments may suggest *Candida* sp. Culture is the only method by which the causative microorganism can be separated and identified. Caution should be used in analyzing culture results, because nails are nonsterile and fungal and bacterial contaminants may obscure the nail pathogen. Periodic acid-Schiff (PAS) staining of nail clippings, using histopathologic processing, may be used as a complementary method for the diagnosis of onychomycosis. Hyphae are seen between the nail layers and lying parallel to the surface [3, 5].

Fungal nail infections can be caused by three different groups of fungi. Most infections are undoubtedly caused by dermatophytes, usually

associated with the involvement of adjacent skin areas; however, nondermatophytic filamentous fungi and yeast also cause onychomycosis. The association between fungi or bacteria in the same nail lesion is very common and can completely change its appearance. To identify the causal agent in each patient and determine cases of multiple etiology are of paramount importance for the treatment, since antifungal drugs have different mechanisms of action [1, 3, 6].

The etiology is variable depending on whether it affects fingernails or toenails. The frequency of yeasts and filamentous fungi (dermatophytes or nondermatophytes) is similar to that found in feet; yeast occurs more frequently in the hands [4, 5].

Tinea unguium (dermatophyte onychomycosis) is caused by dermatophytes. It is an eminently chronic disease characterized by the nail plate detachment from the nail bed, subungual hyperkeratosis, and partial or total destruction of the nail [2, 5, 7]. The species that most often cause onychomycosis are *Trichophyton rubrum* and *Trichophyton mentagrophytes.*

Candida infection of the nail plate most often presents as onycholysis associated with paronychia, although complete destruction of the nail plate and erosion of the distal and lateral nail plate of the fingernails without total nail dystrophy are also seen [1, 2].

Some authors have recommended nail biopsy when it is difficult to diagnose a fungus, mainly when there is a clinical suspicion of saprobic fungus; however, this may not be possible in practice [2].

Therapeutic Approach

The therapeutic advances of recent years with the emergence of drugs for topical, oral, and/or parenteral use, such as amorolfine, ciclopirox, isoconazole, itraconazole, terbinafine, and fluconazole, among others, has promoted treatment success rates, shorter duration of use, and greater safety for patients when compared with the antifungal drugs previously used, such as griseofulvin and ketoconazole. All medications should be prescribed and have its use verified by a dermatologist, since they have the potential to cause adverse effects and more or less severe drug interactions [1, 7].

For the treatment of these diseases it is essential to observe the predisposing and/or aggravating factors that may exist, such as excess moisture, and also to treat any underlying diseases such as diabetes and circulatory problems in the lower limbs [1, 2].

Host factors influencing treatment include age, gender, vascular diseases, diabetes, hypertension, number of toenails infected, infection duration, history of previous treatment, type of onychomycosis, and percentage of nail involvement, nail thickness, presence of dermatophytes, matrix and lateral involvement, and growth rate of the nail [1, 2]. Other factors worth mentioning are inadequate hygiene, frequent traumas on the nails, athlete's foot, prolonged use of moisturizers, excessive sweating, walking barefoot, use of sandals/flip-flops, swimmers' routine, sharing bathrooms and changing rooms, and hot weather. These factors should be taking into account in providing adequate treatment and the need for therapeutic combinations [1, 7].

Onychomycosis that is influenced by host and pathogenic factors requires extensive treatment. The penetration of topical medications into the infected nail bed can be accentuated by the abrasion of the nail or the use of strategies to improve drug permeation using sulfites, hydrogen peroxide, urea, and salicylic acid, among others. Hydrogen peroxide and urea are used in the treatment of nail dermatophytosis and very thick fingernails as well as the abrasion of the affected nail. Slow nail growth caused by tight shoes or circulatory difficulties can be tackled by guidance on the use of proper footwear and hygiene [1, 5].

As onychomycosis treatment may require long-term therapy with oral antifungal and side effects and high costs, it is important to correctly diagnose the infection. Blood tests should be performed and the etiologic agent identified.

Nail Lichen Planus

Introduction

Nail lichen planus (NLP) is a condition that should be diagnosed early. Unless properly treated, it can cause severe scarring. Approximately 10% of patients with lichen planus exhibit ungual alterations, which are commonly found in the nail

apparatus. Although it is not pathognomonic, pterygium is very suggestive of lichen planus and indicates fibrosis in the nail matrix, without nail plate formation due to the development of scar tissue [6, 8].

Concepts

Lichen planus lesions can occur in the fingernails or in areas such as the skin and mucous membranes. It is an inflammatory, autoimmune disease that leads to destruction of basal keratinocytes, causing severe irreversible damage to the nail unit. A genetic susceptibility for lichen planus has been reported in familial cases. This condition has a poor therapeutic response and prognosis, affecting the quality of life of the patient. The etiology has yet to be clarified. It can affect the nails only, or may also involve the oral mucosa and the skin in approximately 10–15% of patients. In adults, NPL may often cause scars [4, 6].

Clinical Presentation

NLP may affect both the bed and the nail matrix of one or more digits. Fingernails are more commonly affected than toenails. Its evolution may vary, and the later diagnosis, nail dystrophy, is more severe, leading to irreversible changes. The proximal nail fold can be affected and can lead to erythema and edema, indicating involvement of the matrix [6, 7].

Matrix involvement causes onychodystrophy with a clinical presentation that ranges from mild to severe, depending on the intensity and duration of local inflammatory change. It is characterized by thinning, longitudinal ridging, and distal splitting of the nail plate. The lunula may be irregularly red in a focal or disseminated pattern as a sign of inflammation. Dorsal pterygium, a scarring process whereby there is growth of the proximal nail fold, may occur. Brown or black pigmentation of the nail (melanonychia) may be transient if the symptoms reverse after treatment. The nails become fragile. Longitudinal ridges (onychorrhexis) may occur as the result of surface fragmentation of the nail blade. Evolution may lead to atrophy and consequent loss of the nail plate. Nail bed involvement is rare, and may

present as subungual hyperkeratosis and detachment of the nail plate (onycholysis) [4, 6].

Diagnosis

The prevalence of NLP in the general population ranges from 0.5% to 1%. It occurs in 10% of patients with disseminated disease. Permanent nail change occurs in more than 4% of patients. It is universal, frequent after the third decade of life, and may affect either children or the elderly. Recent studies have shown that women are affected twice as much as men [6, 8].

Although the clinical examination often presents features for the diagnosis, it may be insufficient. A biopsy of the matrix should be used to confirm the diagnosis. The most common nail findings (Figs. 69.4 and 69.5) are changes in nail surface, fragility of free edge with onycholysis, koilonychia, subungual hyperkeratosis, pterygium, and progressive onychatrophia that can evolve into anonychia. Histopathology may show irregular hyperplasia, accentuated acanthosis,

Fig. 69.4 Striae, onychorexis, dorsal pterygium, erythema, and edema of the proximal nail fold in NLP
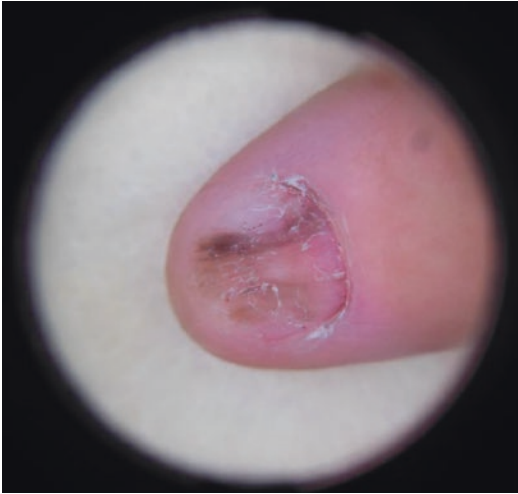
Fig. 69.5 Dermoscopy showing scarring process with pigmentation (melanonychia) in NLP

outbreaks of hypergranulosis, parakeratosis, and vacuolar degeneration of the basal layer. The nail bed can be the site for moderate mononuclear inflammatory infiltrate, with longitudinal ridging and brownish discoloration in the epithelium–nail bed junction [4, 6].

Therapeutic Approach

Treatment of NLP involves corticosteroid infiltration or systemic corticosteroids. The prognosis depends on the degree of matrix involvement. Early diagnosis of NPL is of major importance because of its potential aggression. If untreated, the lesions can lead to a permanent and irreversible dystrophy. Therapy may start with clobetasol enamel and pulse therapy with prednisone [4, 6].

Nail Psoriasis

Introduction

Psoriasis is a chronic inflammatory skin disease that can also affect the nails. It is thought that 80–90% of patients with psoriasis will at some point present with nail involvement [6, 9]. Fingernails are more commonly affected than toenails.

Clinical Presentation

The clinical features of nail psoriasis depend largely on the type of nail tissue affected by the condition. The effects on the nail matrix include Beau lines, pitting, leukonychia, trachyonychia, and onychorrhexis. Effects on the nail bed include onycholysis, salmon patches, oil spots, dyschromias, splinter hemorrhage, and nail bed hyperkeratosis (Figs. 69.6, 69.7, 69.8, and 69.9).

Fig. 69.6 Elkonyxis, onycholysis, and oil spots in a psoriatic nail

Fig. 69.7 Pitting in a psoriatic nail plate

Fig. 69.8 Multiple onycholysis and oil spots in psoriatic nails of fingers

Fig. 69.9 Psoriatic skin lesions in proximal nail fold and pittings in the nail plate

The most common changes that may affect the fingers are pitting, onycholysis, and subungual hyperkeratosis; and the most common in the toes are onycholysis and subungual hyperkeratosis [5].

Diagnosis

The diagnosis is usually clinical. Histopathologic examination may be performed in cases where nail involvement is the only sign. The need for long-term treatment should be considered [11].

All patients should be evaluated for the presence of onychomycosis [6, 10].

Therapeutic

When the disease is limited to the nails, the initial treatment options are high-potency topical corticosteroids, with or without calcipotriol [10].

Clobetasol propionate cream, 0.05% at night [6]

Clobetasol nail lacquer, 0.05–8% three times a week [6]

Triamcinolone acetonide injection (5 mg/mL) into the proximal nail fold, applied monthly [6].

For patients with severe nail disease or for those whose lesions have not responded to treatment, the treatment options are intralesional corticosteroid infiltration or systemic treatment with acitretin, methotrexate, or immunobiological preparations [10].

Periungual Warts

Introduction

This condition is an infectious disease caused by the human papilloma virus (HPV). It is more common in children and adolescents and in persons with onychophagia, in whom the lesions may be multiple [4, 6].

It can evolve into squamous cell carcinoma (SCC). This neoplasm can mimic warts [4].

Clinical Presentation

Periungual warts present as keratotic papules, with black dots representing thrombosed capillaries. When in the nail bed they can cause onycholysis. Wart dissemination occurs by autoinoculation.

Diagnosis

Periungual warts are most often diagnosed by their clinical appearance (Figs. 69.10 and 69.11). The atypical lesions may require histopathologic examination and tests for detection of HPV.

Histopathologic examination should be performed in case of long-lasting warts to exclude SCC [6].

Therapeutic Approach

The choice of treatment modality depends on location, size, number, secondary infection, pain, tenderness, and age.

Topical medications available for the treatment of warts include keratolytic, antivirals, and

Fig. 69.10 Wart with periungual and subungual hyperkeratosis with black spots microthrombi papillae

Fig. 69.11 Hyperkeratosis-related subungual wart

immunomodulatory agents. All have been used successfully; however, the keratolytic agent obtained better outcomes [12].

Salicylic acid at concentrations of 10–50% and trichloroacetic acid in solutions of 50–90% used topically promote peeling and removal of mechanistic particles [6].

Imiquimod inhibits viral replication and activates cellular immunity; 5-fluorouracil has an immunostimulatory action, causing destruction of the lesions [6, 13].

Intralesional bleomycin 0.1% has been used with good therapeutic results [6, 13].

Other therapeutic modalities including cryotherapy, chemical cauterization with salicylic acid, and laser have been used safely [12].

Melanocytic Lesions in the Nail Unit

Concepts

Melanonychia is brown or black pigmentation of the nail unit [14–16]. It has varying etiology, from physiologic lesions to malignant neoplasms. Melanonychias may be total or longitudinal. Longitudinal melanonychias are also called striata, and correspond to the melanin deposit in the nail plate. They are more frequent in the African and Asian population. Its incidence is higher in the over-50 age group, and the first and second fingers are most commonly affected [15]. Melanonychia results from melanin produced by melanocytes in the matrix, where melanocytes are usually quiescent, or by increased activation of melanocytes by nevus melanoma (Figs. 69.12, 69.13, and 69.14) [8].

Clinical Presentation

When striated melanonychia occurs in two or more nails, it may be a sign of a widespread disease (AIDS, Addison disease) or, more often, a result of side effects (chemotherapy, azidothymidine, antimalarials, psoralen/ultraviolet A therapy) [8].

Transverse melanonychia is almost always a result of a pharmacologic treatment.

To make the etiological differentiation of the lesions easier, the "ABCDEF" nail rule and dermatoscopy of the nail plate are increasingly used, while nail bed dermatoscopy is a promising test [16, 18].

Fig. 69.12 Longitudinal melanocytic nail lesion smaller than 3 mm

Fig. 69.13 Longitudinal melanocytic nail lesion smaller than 3 mm seen under polarized light dermoscopy (Dermlite)
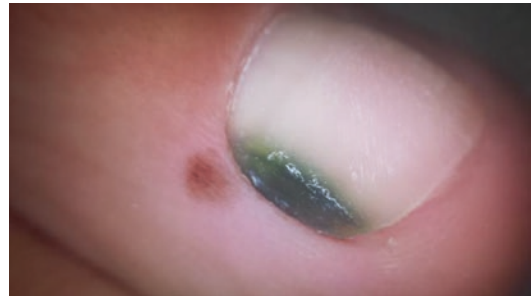
Fig. 69.14 Chromonychia (greenish) affecting the lateral edge of the longitudinal nail plate, suggestive of bacterial contamination. Note a nevus on the lateral nail fold

Diagnosis

The ABCDEF rule is useful for differentiating benign from malign melanonychia (see Box 69.1).

Box 69.1 ABCDEF and Suspect of Malign Melanonychia

A. Age	50–70 years; African and Asian origin
B. Band	Over 3 mm; brown, black
C. Change	Nail band; nail morphology
D. Digit involved	Thumb, hallux, single
E. Extension	Hutchinson's sign
F. Family and personal history	Dysplastic nevus syndrome or previous melanona

Despite the major assistance of the ABCDEF rule and lesion dermatoscopy, histopathology still is indispensable in cases of uncertainty. The proposed treatment will depend on the etiology of each case.

Tumors in the Nail Unit

Concepts

Tumors are grouped into nonpigmented benign lesions (glomus tumor, myxoid cyst, nail keratoacanthoma) and malignant lesions (SCC and Bowen disease, onychomatricoma, nail melanoma).

Myxoid Cyst

This lesion is found in the distal phalanx of the finger, and may involve the nail matrix. It is sometimes painful and is often associated with degenerative changes in the distal joints and the presence of Heberden nodes, osteoarthritis, and bone spurs. Digital myxoid cysts occur most frequently in persons between the ages of 40 and 70 years (Fig. 69.15). The diagnosis is made by means of anamnesis and clinical examination of characteristic lesions [1]. Differential diagnoses include xanthoma, epidermoid inclusion cyst, and molluscum contagiosum, among others [6].

Fig. 69.15 Myxoid cyst. Lesion in dorsal portion of finger

Some treatment approaches include aspiration with drainage, instillation of corticosteroids, cryosurgery, electrocoagulation, and surgical excision [6]. Surgical complications include infection, recurrence, onychodystrophy, edema, pain, and stiffness [6].

Glomus Tumor

This is a rare benign neoplasm that arises from the neuroarterial structure called a glomus body, an arteriovenous shunt within the dermis that contributes to temperature regulation of the fingers. The branching vessels become surrounded by myoepithelial cells, forming perivascular cuffs called Sucquet-Hoyer channels [6, 19]. They occur in women more than in men [6]. Usually, these tumors present as a small, reddish blue nodule measuring up to 2 cm (Fig. 69.16). Ungual alterations are frequently observed. Clinically the lesions are characterized by intense, pulsating, and debilitating pain. Clinical diagnosis is done by the classical triad of paroxysmal pain, hypersensitivity to temperature changes, and local sensitivity (Box 69.2) [6].

Fig. 69.16 Glomus tumor with reddish painful blue spot in the lunula

Box 69.2 Glomus Tumor Triad
- Paroxysmal pain
- Hypersensitivity to temperature changes
- Local sensitivity

Several clinical tests are useful for diagnosing glomus tumors: (1) tourniquet, puncture; (2) radiography; (3) dermatoscopy; (4) ultrasonography; and (5) magnetic resonance imaging (MRI). Histologic assessment of tumors is regarded as the gold standard in this respect. Complete surgical excision (Figs. 69.17 and 69.18) is the recommended treatment for glomus tumors to avoid recurrence [6, 17, 19, 20].
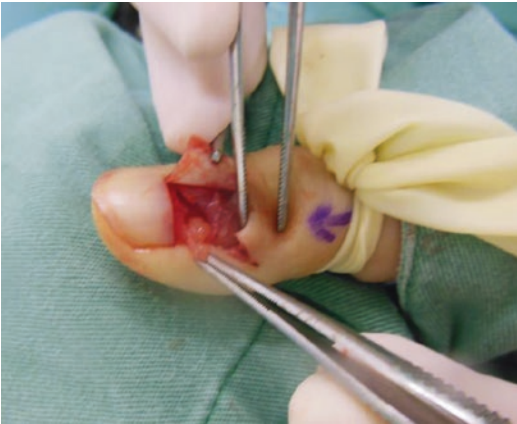
Fig. 69.17 The lobuled tumor is located below the nail bed attached to the bone

Fig. 69.18 Immediate appearance after suture

Nail Keratoacanthoma

Keratoacanthoma is a low-grade skin tumor that rarely affects the nail apparatus [1]. Middle-aged men are more at risk. It can be solitary, multiple, eruptive, or familial. The clinical feature differs from that of traditional keratoacanthoma, as in the subungual form there is usually pain, early and fast growth, and underlying bone compression [21]. The diagnosis is made by clinical and complementary examinations.

The differential diagnosis of a painful and nodular lesion in the distal phalanx includes dermoid cyst, common wart, subungual exostosis, amelanotic melanoma, SCC, and subungual keratoacanthoma. Radiologically the subungual keratoacanthoma is almost indistinguishable from subungual SCC. Nonetheless, keratoacanthoma causes a lesion in the distal phalanx that has well-defined borders and grows but does not penetrate the bone. Furthermore, keratoacanthoma usually occurs in the fifth decade of life, whereas SCC usually occurs in the seventh decade [21]. Treatment includes curettage and local excision.

Squamous Cell Carcinoma and Bowen's Disease

SCC is a malignant neoplasm originating from the epithelial cells of the skin and mucosa. This neoplasm is characterized by variable clinical features (Fig. 69.19) and an indolent clinical

Fig. 69.19 Squamous cell carcinoma of the nail bed causing destruction of the nail plate

course. Bowen disease is a squamous cell carcinoma in situ. It affects all races and is more frequent in males in the fifth and sixth decades of life. The etiopathogenesis has not been confirmed. Several factors are involved: trauma, chronic infections, immune suppression, congenital diseases, exposure to radiation, and infection by the HPV [6].

Biopsy is the gold standard for the diagnosis. The treatment is surgical and may include a limited to digital amputation, depending on the tumor and extension of bone involvement.

Onychomatricoma

Onychomatricomas are rare benign tumors originating from the nail matrix and underlying stroma, affecting middle-aged men and women evenly. It is more prevalent in Caucasians [6].

The condition is usually asymptomatic; however, the key clinical feature for the diagnosis is the presence of a yellowish longitudinal band of variable thickness (Fig. 69.20) [22].

Additional tests may help confirm or rule out the diagnosis, such as dermatoscopy, ultrasonography, and MRI. The biopsy of the lesion is crucial for a definitive diagnosis, which is histologic. Effective treatment is complete surgical excision (Fig. 69.21), and the long-term prognosis is favorable [17, 22].

Fig. 69.20 Onychomatricoma of the right index showing yellowish appearance of striations
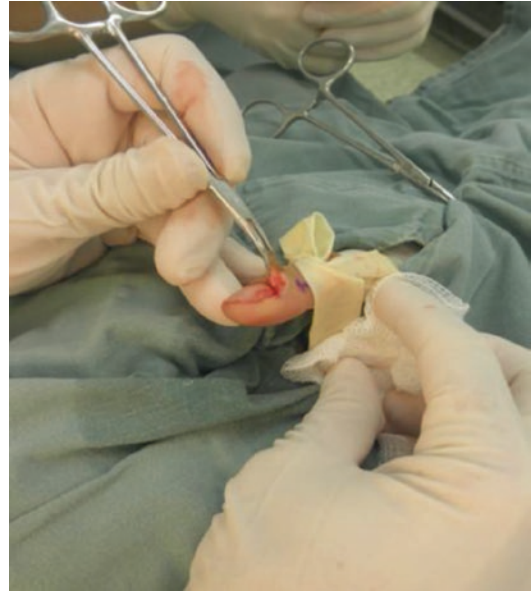
Fig. 69.21 Surgical resection of the tumor

Nail Apparatus Melanoma

Nail apparatus melanoma (NAM) is a rare melanocytic neoplasm, with an average 5-year survival rate of 56% in developing countries [6]. NAM is more commonly seen as longitudinal melanonychia, which can also be a clinical manifestation of other ungual apparatus changes that cause ungual matrix melanocytic activation (Fig. 69.22). The pigmented bands due to continuous growth of the nail plaque can be seen in ungual matrix nevi alongside benign melanocytic hyperplasia and inflammatory, traumatic, and iatrogenic changes.

Hirata et al. have suggested that the use of intraoperative dermatoscopy on the nail bed and matrix with polarized light could result in better visualization of pigmented lesions, since this examines the region of melanin production. Although this is an invasive technique it could give the best level of diagnostic accuracy when compared with clinical examination, ABCDEF rules, and traditional dermatoscopy (Fig. 69.23) [23].

Histopathology is still the gold standard, and biopsy can be incisional or excisional [3]. Although there is no current consensus on managing ungual melanoma in situ, surgical excision

Fig. 69.22 Longitudinal melanonychia on the right distal phalanx of the finger

Fig. 69.23 Traditional dermatoscopy shows irregular pigmentation of the nail plate

Fig. 69.24 Severe ingrown toenail

Fig. 69.25 Bilateral ingrown toenail

entails the complete ungual apparatus itself, including the nail plaque, bed, and matrix [17, 23]. The resulting defect can be corrected with a partial or total skin graft.

Ingrown Toenail

Concepts

An ingrown toenail is a multifactorial inflammatory condition that may cause severe discomfort and pain to the patient. Ingrown toenails result from an imbalance between the width of the nail plate, the nail bed, and lateral nail fold hypertrophy [24, 27].

Clinical Presentation

Ingrown toenails (Figs. 69.24 and 69.25) can be classified into four types: ingrowing toenail in infancy, lateral and distal nail fold hypertrophy, pincer nails, and juvenile ingrown toenail.

Ingrown Toenail in Infancy

1. Distal toenail embedding with normally directed nail

This condition consists of congenital hypertrophy of the distal tissue. In most cases, conservative

treatment with massage of the distal nail wall in a distal-plantar direction is effective. This condition usually resolves up to 6 years of age [6, 24, 26].

2. Congenital hypertrophic nail fold of the hallux

Most frequently, the medial nail fold is hypertrophic. This condition may resolve spontaneously after several months. In persistent cases, resection of the hypertrophic nail fold is indicated [6, 24, 26].

3. Congenital malalignment of the hallux nail

This condition is characterized by a thickened, triangular, discolored, oyster-shell-like nail.

When the deviation is small, with hardening of the nail, distal locking disappears; when the deviation is severe, surgical rotation of the nail matrix is required [24, 26].

Lateral and Distal Nail Fold Hypertrophy

The nail plate exerts pressure on the nail folds, keeping its anatomic shape. When the nail plate is absent, the pulp of the hallux is dislocated dorsally during foot gait, leading to nail fold hypertrophy. Treatment consists of surgical removal of hypertrophic nail folds, allowing for physiologic growth of the nail plate [24, 26].

Pincer Nails

This condition is characterized by transverse overcurvature of the nail plate. In most cases, the overcurvature is bilaterally symmetric and combined with lateral deviation of the long axis of the nail. Radiography is an essential diagnostic tool, often revealing osteophytes [24, 26].

Juvenile Ingrown Toenail

This condition results from an imbalance between the width of the nail plate and that of the distal portion of the nail bed. Contributing factors include convex nail clipping, overcurvature of the nail plate, toe rotation, and wearing inappropriate shoes [6, 24, 26].

Juvenile ingrown toenail can be classified into three clinical stages [24, 26]

1. Erythema, edema, and pain on pressure
2. Purulent drainage and infection
3. Purulent granulation tissue and lateral nail hypertrophy

Therapeutic Approach

Conservative Treatment

The decision to adopt a conservative treatment approach depends on the clinical aspect of the ingrown toenail. This approach is indicated in the following cases: absence of lateral nail fold hypertrophy, presence of mild distal nail fold hypertrophy, and presence of mild transverse overcurvature of the nail [26].

General measures: wearing wide shoes or walking barefoot and correcting nail trimming [24].

The clip system: a plastic brace is glued crosswise to the nail and maintained for 3–4 weeks. The goal is to correct the transverse overcurvature of the nail. This method promotes fast pain relief [24, 26].

Placing wisps of cotton on lateral nail folds protects the nail spike and allows the nail plate to grow without traumatizing the surrounding tissue [26].

Gutter treatment: consists of inserting a longitudinally sectioned vinyl tube into the lateral nail margin. This procedure is performed under local anesthesia [24].

Tape is used to pull the lateral nail fold laterally. This method should be performed daily [6, 24, 26].

Acrylic artificial nails are placed over ingrown nails to push the lateral nail folds laterally and decrease hypertrophy [24, 26].

Surgical Treatment

Surgery is indicated when conservative treatments fail or in moderate and severe cases.

Definitive Narrowing of the Nail Plate

1. Chemical cauterization

This treatment is indicated for stage 2 and 3 ingrown toenails and for pincer nails at any stage. In the latter, the procedure will relieve the pinching effect on the underlying tissue. In

pincer nails with hyperostosis of the distal tuft, this technique is beneficial in the presence of pain on lateral pressure. When pain on downward pressure is present, other techniques are indicated [25, 29].

Phenol cauterization is a simple but highly effective method for treating ingrown nails, with success rates as high as 95% [24, 29]. Phenol is a necrotizing, disinfecting, anesthetic agent. It causes tissue destruction, disinfects the surgical field, and improves postoperative patient comfort (phenol induces demyelination of terminal nerve endings for several weeks) [6].

Distal digital block anesthesia is administered with lidocaine 2% without epinephrine. When granulation tissue is present, it should be removed to improve visualization of the lateral margin of the nail plate. A lateral strip of nail is cut longitudinally and avulsed, allowing access to the lateral horns of the matrix. When necessary, the nail matrix, the nail bed, and the lateral nail folds are gently curetted to remove debris. A tourniquet is applied and a cotton swab with phenol 88% is rubbed vigorously over the area for 1–3 min [24, 25, 27, 30].

Phenol will be inactivated with the blood flow after release of the tourniquet. Some authors use alcohol to do this [6, 28]. Oozing will appear on the third postoperative day and continue for up to 2–4 weeks. Frequent washing of the wound prevents infection and accelerates healing [1, 3]. Antibiotic therapy is indicated when infection is present [24, 25, 27, 28].

2. Wedge resection

This treatment is technically more challenging. A lateral strip of nail is avulsed and an oblique section is performed on the proximal nail fold to allow nail fold elevation and visualization of the lateral horn of the matrix. The horn is then meticulously dissected from the bone. Pain and a high postoperative infection rate (20%) [24, 28] are drawbacks of this technique.

Debulking of Periungual Soft Tissues

This procedure is indicated when an ingrown nail is caused by hypertrophy of the nail folds. There are two main debulking surgical approaches.

1. Howard–Dubois procedure

Distal digital block with lidocaine 2% without epinephrine is administered followed by application of a tourniquet. A crescent of soft tissue is removed with a fish-mount incision performed parallel to the distal groove, around the tip of the toe. The first incision is made 5 mm below the distal and lateral grooves. The second incision is made so as to create a wedge of 3–5 mm at its greatest width in the middle of the distal wall. Both fat and fibrous tissue should be removed. The wound should be closed using simple interrupted stitches (4.0 or 5.0 nylon). The major complication of this procedure is necrosis by overtight suturing. The postoperative period is painful, requiring good pain control. Stitches are removed after 10–14 days [25, 27, 29].

2. Super U procedure

This technique described by Eval Rosa is indicated in cases of severe hypertrophy of nail folds. Eligible patients should be informed of the long healing time (up to 2 months). A U-shaped incision is performed starting at the proximal edge of one of the lateral nail folds, running through to the distal nail fold, and ending on the other side of the lateral nail fold. All hypertrophic tissues are removed. Running locked suture with 3.0 or 4.0 nylon is performed to avoid bleeding [25, 27, 29]. Pain is severe in the first 48 h. Mild opioid-type narcotic pain medications should be prescribed.

Paronychia

Concepts

Paronychia is an inflammatory disorder affecting the proximal and lateral nail folds, usually caused by trauma to the cuticle, which is the physical barrier between the nail plate and nail folds [7, 30]. Trauma can result from ordinary events, such as dishwashing, nail biting, finger sucking, an ingrown nail, or other types of nail manipulation [30, 31]. When the cuticle separates from the nail plate, an inflammatory reaction may occur as a result of the penetration of infectious organisms,

allergens, or irritants [30, 31]. The pathogen most commonly associated with paronychia is *Staphylococcus aureus*, but cases infected by *Streptococcus pyogenes*, *Pseudomonas pyocyanea*, and *Proteus vulgaris* have also been reported [30–32].

Paronychia can be classified into acute or chronic. Acute paronychia is characterized by the rapid onset and evolution of symptoms after the trauma. Chronic paronychia is a multifactorial inflammatory reaction lasting longer than 6 weeks [30–32]. Chronic paronychia is common in housewives, bartenders, and kitchen workers, whose work activities require frequent hand contact with water and detergents [6, 30].

Acute Paronychia

Clinical Presentation

The affected digit is painful, showing erythema and swelling of the proximal and lateral nail folds [30, 31]. Patients initially present with accumulation of purulent material under the nail fold. Subungual abscess with pain and inflammation of the nail matrix can occur if the infection remains untreated [6, 30, 31].

Diagnosis

The diagnosis of acute paronychia is based on history of minor trauma and physical examination findings.

The digital pressure test may be useful to detect the condition in early stages. The test is performed by applying light pressure to the distal volar aspect of the affected digit. The increase in pressure within the nail fold (particularly in the abscess cavity) causes blanching of the overlying skin and clear demarcation of the abscess.

In moderate and severe cases, it is important to identify the responsible agent and rule out infections caused by methicillin-resistant *S. aureus* [6, 29, 30].

Therapeutic Approach

Clinical treatment [6, 30, 31]:

1. Soaking the affected digit in warm water and in Burow's solution
2. Mild cases: antibiotic cream (gentamicin, mupirocin, fusidic acid) alone or in combination with topical corticosteroid
3. Persistent lesions: oral antistaphylococcal antibiotic therapy

Surgical treatment is recommended when an abscess is present [6, 7, 21, 30]:

1. Superficial infections: easily drained with a size-11 scalpel or by lifting the nail fold with the tip of a 21- or 23-gauge needle
2. Severe cases: removal of the proximal third of the nail plate

Preventive measures are listed in Box 69.3.

Box 69.3 Recommendations for Preventing Acute and Chronic Paronychia [7, 30]

1. Avoid moist environments, chronic microtrauma, and contact with irritants or allergens (for at least 3 months once the condition is resolved)
2. Wear cotton gloves under rubber gloves during manual work
3. Avoid aggressive nail procedures (e.g., manicuring)
4. Keep nails short
5. Keep affected areas clean and dry

Chronic Paronychia

Clinical Presentation

In chronic paronychia, erythema is less intense than in acute paronychia. Other clinical manifestations include tenderness and swelling, with retraction of the proximal nail fold and absence of the adjacent cuticle (Fig. 69.26). Pus may form bellow the nail fold.

Fig. 69.26 Chronic paronychia, dystrophic nails, and onychomycosis

Usually several fingernails are affected. Colonization by *Candida albicans* or bacteria may occur [6, 30].

Diagnosis

Chronic paronychia is diagnosed based on clinical findings present for at least 6 weeks, history of trauma, frequent contact with detergents or other chemicals, or systemic drug therapy (retinoids, antiretroviral agents, antiepidermal growth factor receptor antibodies) [4, 26, 30].

In cases that do not respond to treatment, differential diagnosis with squamous cell carcinoma, malignant melanoma, and metastases from malignant tumors should be performed.

Therapeutic Approach

Clinical Treatment

Exposure to irritants should be avoided. Topical steroids are the first-line therapy; tacrolimus 0.1% ointment is an alternative option [6, 30].

Topical treatment with a steroid and an antifungal agent combined may be used, but data showing the superiority of this combined treatment in relation to steroid therapy alone are lacking [30, 31].

In refractory cases, monthly intralesional injections of triamcinolone acetonide (2.5 mg/mL) may be used.

Surgical Treatment

Surgery is recommended when the associated fibrosis does not improve with clinical treatment [6, 30, 33].

En bloc excision of the proximal nail fold (4–5 mm) is effective.

Recently, the square flap technique has been proposed to treat chronic fibrosis caused by paronychia. The technique consists of incising the proximal nail fold, exposing the fibrosis, and removing it carefully, so as to prevent damage to the nail matrix [33].

Preventive measures are listed in Box 69.4.

Box 69.4 Recommendations for Preventing Acute and Chronic Paronychia [7, 30]

1. Avoid moist environments, chronic microtrauma, and contact with irritants or allergens (for at least 3 months once the condition is resolved)
2. Wear cotton gloves under rubber gloves during manual work
3. Avoid aggressive nail procedures (e.g., manicuring)
4. Keep nails short
5. Keep affected areas clean and dry

Glossary

Chromonychia Abnormalities of color depend on the transparency of the nail, its attachments, and the character of the underlying tissue.

Hutchinson's sign Extension of melanocytic pigment to lateral, proximal, and distal folds, adjacent to the nail plate.

Koilonychia A transverse and longitudinal concave nail dystrophy giving a spoon-shaped appearance.

Melanonychia A black or brown discoloration of the nail, usually localized and often longitudinal.

Onychomycosis A fungal infection of the nail apparatus.

Pitting Pits are small erosions in the nail surface.

PUVA therapy PUVA is a combination treatment used for severe skin diseases consisting of psoralens (P) followed by exposure of the skin to UVA (long-wave ultraviolet radiation).

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Metatarsalgia, Calluses, and Callosities of the Feet

70

Silvio Maffi

Key Points Summary
- Metatarsalgia is localized or diffuse pain in the metatarsal heads
- Metatarsalgia can be classified as primary metatarsalgia resulting from a functional or postural condition, or secondary metatarsalgia resulting from a metabolic, neurologic, traumatic, or iatrogenic condition
- Hyperkeratosis expresses increased activity of keratinocytes in a callus or callosity, where it results from epidermal intermittent mechanical stimulation due to friction or increased pressure
- Callus or heloma is a reactive hyperkeratotic lesion of the skin located in well-defined friction or stress points with well-delimited edges, painful to direct local palpation
- Callosity or tyloma is a larger hyperkeratotic reactive lesion than the callus. It can be seen in larger areas of friction and stress, with more subtle margins, which usually encompass a wider area and show painful and more diffuse symptoms.

- The correct assessment of the etiology and diagnostic differentiation deeply influences the type of therapeutic approach.

Concepts

Metatarsalgia and plantar pain are frequent complaints of modern humanity. Bipedalism, paved ground, footwear and its peculiar variations, and many other evolutionary changes have created an array of factors that favor lesion development, deformities, and pain in the anterior and plantar regions of the human foot.

Calluses and callosity are the most often found hyperkeratotic wounds in the feet. These lesions are strongly related to contact with, friction against, and strain on the feet when individuals walk, jump, and wear shoes. For this reason it is important to distinguish calluses and callosity from other hyperkeratotic lesions that develop on the feet, such as plantar warts, eccrine poroma, arsenical keratosis, plantar keratodermas, and porokeratosis, since the treatment of these lesions requires a totally different approach (Box 70.1).

Metatarsalgia, calluses, and callosities are closely related. They are usually part of the same clinical presentation of the patient's complaint of foot pain and/or hyperkeratosis, as metatarsalgia usually expresses a reactive hyperkeratotic lesion.

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Box 70.1 Foot Hyperkeratoses: Main Causes

Bone Causes
Protruding metatarsal condyle
Long metatarsos
Post-traumatic deformities
Congenital foot deformities
Toe deformities

Systemic Diseases
Arthritis rheumatoid
Psoriatic arthritis
Gout

Dermatologic lesions
Plantar warts
Eccrine poroma
Plantar porokeratosis
Keratoderma
Arsenical keratosis
Epithelioma cuniculatum (verrucous carcinoma)
Seborrheic keratosis (stucco keratosis)

Tissular Causes
Plantar fat pad atrophy
Plantar scars

Latrogenic Causes
Unsuccessful metatarsal surgeries
Unsuccessful toe surgeries
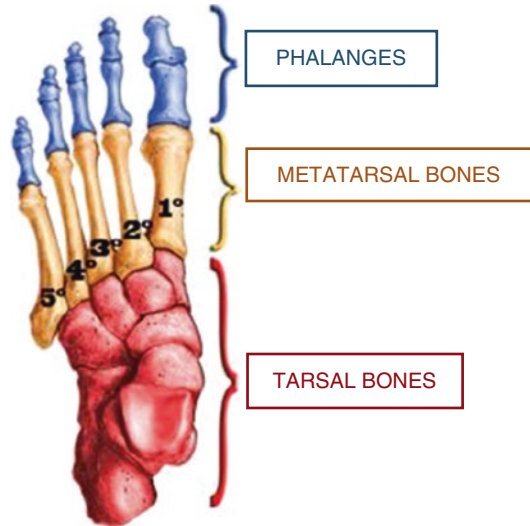
Fig. 70.1 The metatarsal, tarsal, and phalangeal bones
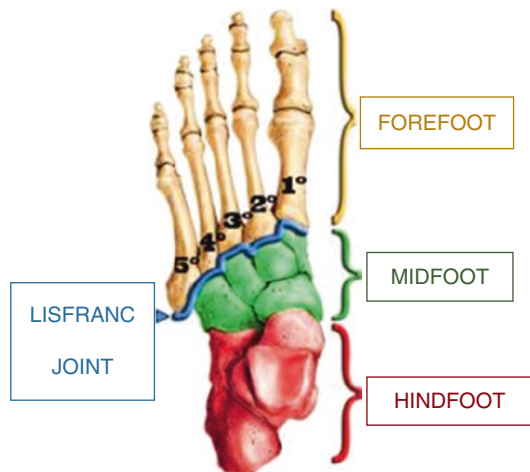
Fig. 70.2 Forefoot, midfoot, and hindfoot

Anatomic and Biomedical Considerations of the Foot

The foot can be anatomically divided into the metatarsal, tarsal, and phalangeal bones. The tarsus encompasses the calcaneus, talus, navicular, and cuboid bones, and the three cuneiform bones. The five metatarsal bones connect the tarsus to the phalanges that make up the foot (Fig. 70.1).

Another anatomic division that takes functionality into account divides the foot into forefoot, midfoot, and hindfoot. The forefoot includes the five toes and the five metatarsal bones; the midfoot includes the navicular, cuboid, and three cuneiform bones; and the hindfoot includes the calcaneus and talus (Fig. 70.2).

It is in the forefoot that most calluses develop, in addition to callosity and plantar warts, since it comprises a large and important foot support area, besides having joint mobility of the toes and many bone prominences that cause direct contact with footwear.

The joint line dividing the midfoot and the forefoot is called the tarsal–metatarsal joint or Lisfranc joint. It is responsible for the movements of plantar flexion, dorsal flexion, and metatarsal pronation and supination (Fig. 70.2).

The metatarsal bones are long bones that show a distal protrusion that joins the toe proximal phalanges, the so-called metatarsal heads. They make up important plantar pressure points, mainly the second and third metatarsal bones, usually longer than the first metatarsal bone.

The metatarsal bone length may show anatomic variation and make up one of the three patterns specified as follows, known as metatarsal formulae:

Index Plus type: 1 > 2 > 3 > 4 > 5 (Fig.70.3).
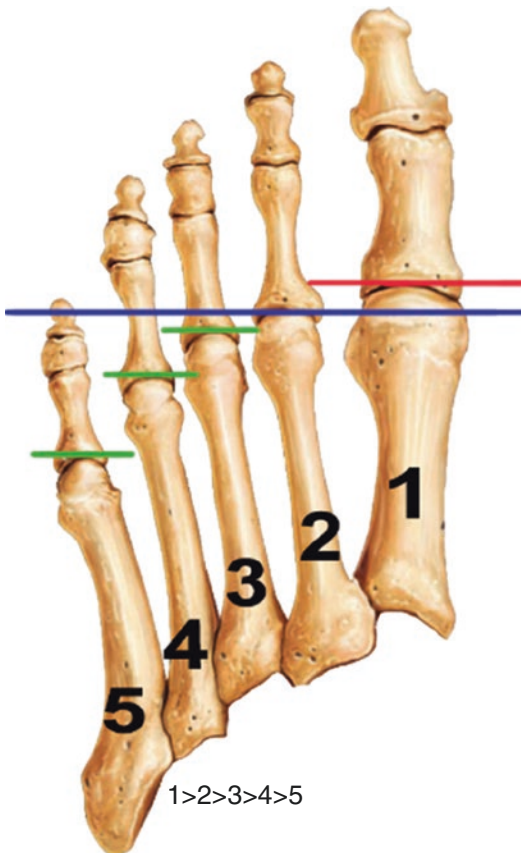
Index Plus-Minus type: 1 = 2 > 3 > 4 > 5 (Fig. 70.4)

Index Minus type (A): 2 > 1 > 3 > 4 > 5 (Fig. 70.5) or (B): 2 > 3 > 1 > 4 > 5 (Fig.70.6)

The most commonly found pattern in the population is the index minus type (approximately 60%) (2 > 1 > 3 > 4 > 5) [1].

Under the metatarsal heads the plantar plaque can be observed, as well as the toe flexor tendons and the plantar fat pad. These structures are important for joint movement and stabilization of the toes, in addition to absorbing the impact and pressure resulting from body weight unloading on the ground. The plantar plaque is a fibrocartilaginous structure included in the metatarsal-phalangeal joint capsule. It hinders toe hyperextension and is extremely resistant to tensile strength involved in the gait mechanism (Fig. 70.7).

Fig. 70.3 Index Plus type
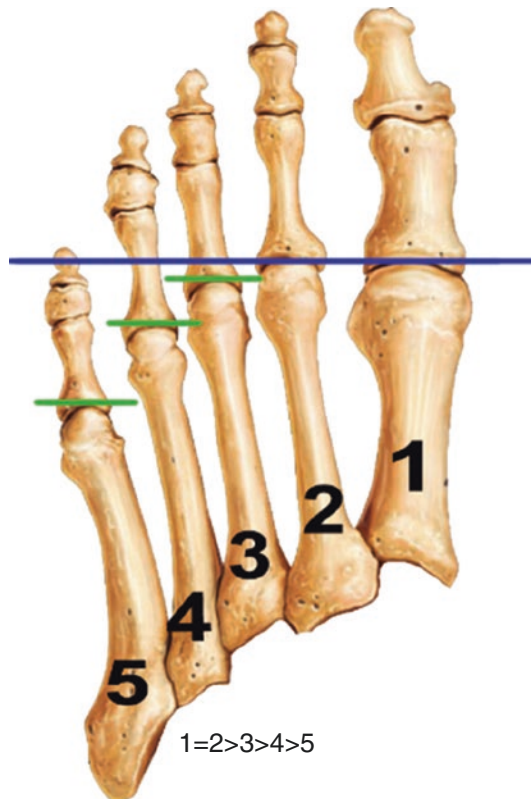
Fig. 70.4 Index Plus-Minus type
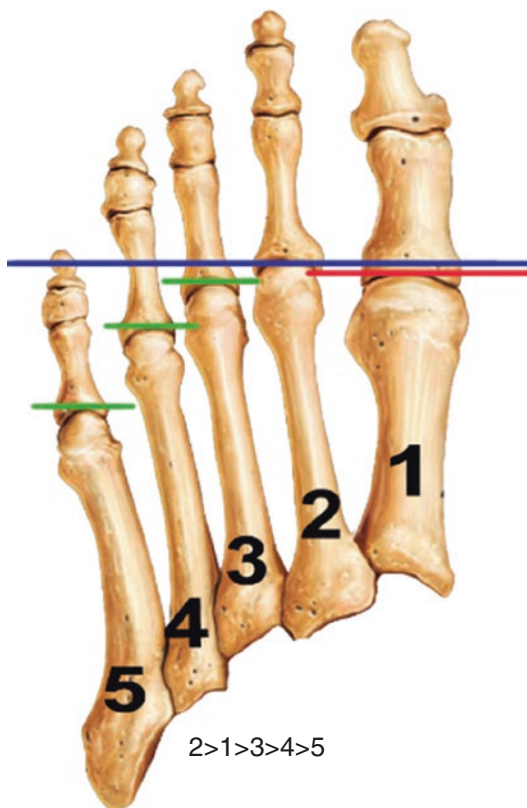
Fig. 70.5 Index Minus type A

The hallux is the great toe which, different from the others, has two sesamoid bones inserted into its plantar plaque, known as the glenosesamoid complex or apparatus. They strengthen the hallux joint stability, act as pulleys for the flexor tendons, and represent two support points under the head of the first metatarsal bone (Fig. 70.8).

The plantar fat pad runs from the calcaneus to the toe bases, displaying a unique septal configuration. Small ligaments cross the fat tissue and connect the skin to the deepest connective tissue, therefore creating resistant compartments that hinder fat displacement when the feet undergo strain (Fig. 70.9).

The biomechanics of the foot are very complex. Bones, muscles, and tendons act in a dynamic mechanism, with oscillations between gait phases. This joint system confers stability, strength, and impulse thus attenuating strain, absorbing impact, and allowing the necessary stability for the feet to adapt to ground irregularities.

Fig. 70.6 Index Minus type B
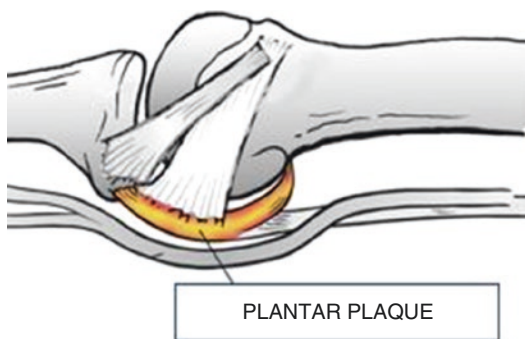
Fig. 70.7 Fibrocartilaginous structure and the gait mechanism
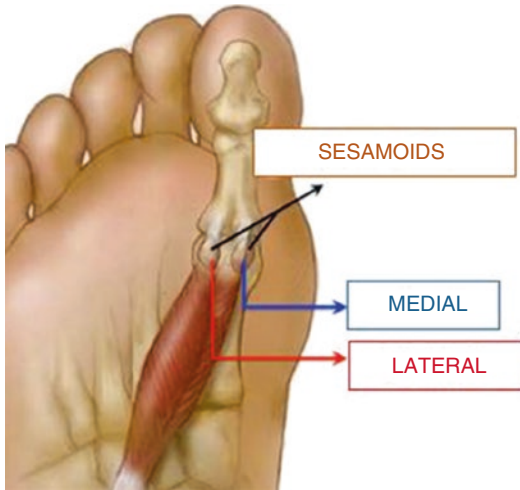
Fig. 70.8   Glenosesamoid complex

Fig. 70.9   Plantar fat

The hindfoot and midfoot joints have a small movement range that guarantees them mechanical stability and support. The forefoot, however, has the greatest mobility, mainly the fourth and fifth metatarsal bones, an important feature for foot balance and adjustment. On the other hand the first, second, and third metatarsal bones have movements limited at the Lisfranc joint level; they are stronger, more stable, and support a large part of the forefoot. Being longer and firmer, these three metatarsal bones create compression points under their heads that can result in calluses or callosities, depending on the footwear, physical activity, or any other factor that changes the normal distribution of the body weight [2].

During the gait support phase, the center of the plantar pressure moves rapidly from the calcaneus to the metatarsal bones where it remains more than 50% of the time before going toward the toes. Therefore, any change or abnormality of the forefoot, either local or diffused, may result in plantar calluses or callosity development [3].

Clinical Presentation

Metatarsalgia is the localized or generalized pain in the region of the metatarsal heads. It can be classified as primary metatarsalgia, i.e., functional or postural, or secondary metatarsalgia, i.e., metabolic, neurologic, traumatic, or iatrogenic [4, 5]. Hyperkeratosis represents increased activity of keratinocytes, as occurring in a callus or callosity, where hyperkeratosis results from the intermittent mechanical stimulation of the epidermis by friction or increased pressure. Callus, or heloma, is a reactive hyperkeratotic skin lesion located in well-defined friction and pressure points with well-delimited edges, painful to direct local palpation (Fig. 70.10).

Fig. 70.10   Reactive hyperkeratotic skin

Fig. 70.11 Callosity (tyloma)

Fig. 70.12 Metatarsal plantar flexion

Callosity, or tyloma, is a larger hyperkeratotic reactive lesion than the callus. It is located in larger areas of friction and pressure, with more subtle margins which usually encompass a wider area, and shows painful and more diffuse symptoms (Fig. 70.11).

Metatarsalgia, calluses, and callosities are closely related. They are often seen as a an overall clinical presentation in a patient who complains of pain and/or foot hyperkeratosis, since metatarsalgia expresses a hyperkeratotic reactive lesion.

Primary Metatarsalgia

Primary metatarsalgia includes conditions that alter the metatarsal basic anatomy, the reciprocal relationship of the metatarsal bones, and how they relate to the other toe bones.

The main cause of primary metatarsalgia involves the *Index Minus* type metatarsal pattern, where the second and/or the third metatarsal bones are longer than the hallux and, therefore, more susceptible to the local increased plantar pressure during the gait impulse phase, when there is rolling and detachment of the forefoot.

The second most common cause of primary metatarsalgia is plantar displacement, or plantar flexion, of one or more metatarsal bones. This changes load distribution and leaves a localized pressure on the flexed head(s), resulting in varied size callosities on the forefoot plantar region. The metatarsal plantar flexion is usually observed as a result of claw deformity in one or more toes which pushes the metatarsal head toward the ground, owing to the anatomic change and imbalanced tendon forces (Fig. 70.12).

Another cause is the congenital postural changes of the feet, such as cavus and equinus deformity of the foot which results in a generalized metatarsal mechanic overload. Cavus deformity results in a decreased support surface that entails an area of plantar hyperpressure (Fig. 70.13). The equinus foot, on the other hand, promotes this increased pressure because of triceps surae muscle contracture that results in forced flexion of the forefoot toward the ground (Fig. 70.14).

Primary metatarsalgia may occur as a result of congenital deformities of the head itself, or the metatarsal condyles. An ill-formed, enlarged head or a more protruding condyle can result in pain and callosity on the plantar aspect.

It is worth noting that together with the causes of primary metatarsalgia, the increased pressure under the metatarsal heads is excessively intensified, with an impact on physical activities and the use of thin-soled or high-heeled shoes.

Fig. 70.13 Normal and cavus foot
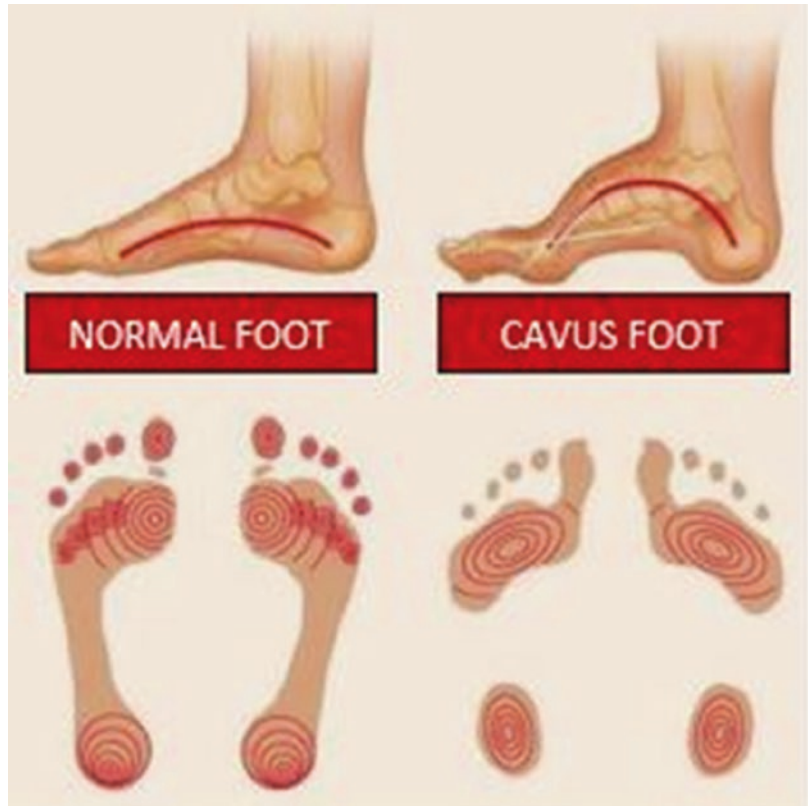
Fig. 70.14 Equinus foot

Secondary Metatarsalgia

Secondary metatarsal pain is caused by different clinical conditions that indirectly give rise to deformity and generate mechanical overload or inflammatory processes in the forefoot region. However, secondary metatarsalgia is not always associated with plantar calluses or callosity development.

Inflammatory diseases, such as rheumatoid arthritis, psoriatic arthritis, and gout, may cause chronic synovitis and bursitis that degenerate the joint capsule and impair the toes. This deformity brings about the anterior displacement of the plantar fat pad and leaves the metatarsal heads unprotected against ground impact. Moreover, the inflammatory disease itself may cause plantar fat atrophy, decreasing its thickness (Fig. 70.15).

Fig. 70.15 Inflammatory disease and secondary metatarsalgia

Fig. 70.16 Compressive disorder

Fig. 70.17 Avascular necrosis (Freiberg's disease)

Avascular necrosis of the metatarsal head, known as Freiberg's disease, is a local circulatory disease that causes deformity of the metatarsal phalangeal joint and entails pain and movement loss. More frequently it impairs the head of the second metatarsals (Fig. 70.17).

Sequelae of metatarsal fractures, such as fragmented poor alignment, metatarsal shortening, head elevation, or plantar flexion, create hyperpressure points and cause changes in the plantar load distribution.

Iatrogenic metatarsalgia more often occurs after surgical procedures involving osteotomies. Poorly aligned corrections, exaggerated or inappropriate bone resection, and poor consolidation of a bone section may bring about deformities, loss of joint movement, and metatarsal pain. They may also lead to calluses or callosities, frequently noticed after surgeries that change the metatarsal formula and displace support points from one metatarsal bone to the neighboring metatarsal bone, resulting in a condition known as transfer metatarsalgia (Fig. 70.18).

Compressive neurologic diseases, such as Morton's neuroma (benign tumoral process of the plantar toe nerve) and tarsal tunnel syndrome (compression of the tibial nerve), may cause pain and paresthesia in the metatarsal plantar region (Fig. 70.16).
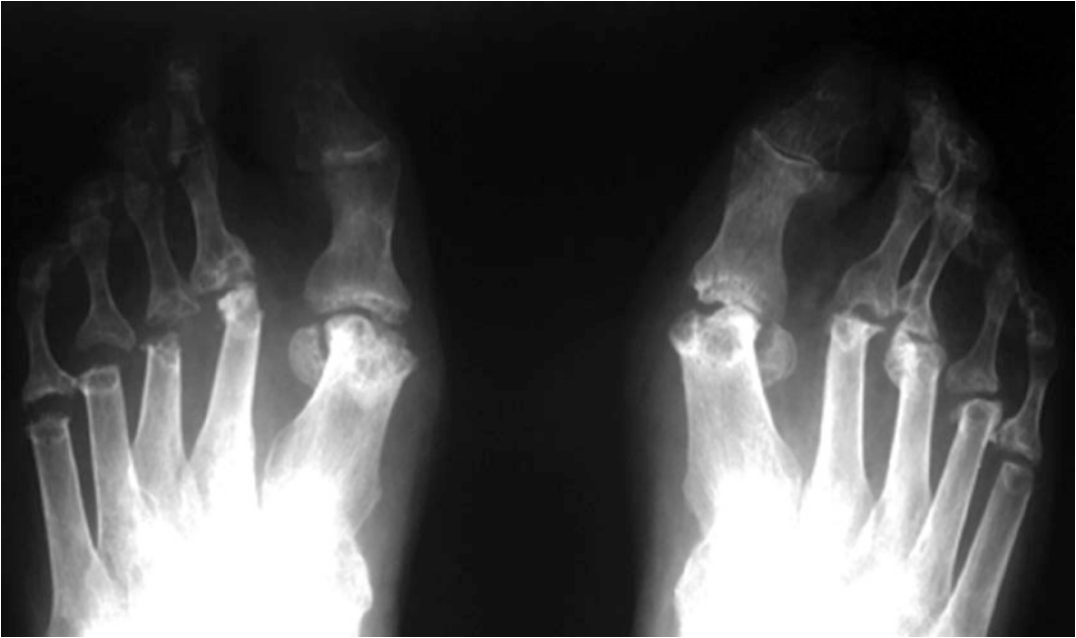
Fig. 70.18 "Transfer" metatarsalgia

Calluses (Helomas)

Calluses may be present in many foot locations. They usually occur where bone protuberances can be noticed, such as the joints and the metatarsal heads, which develop points and mechanical attrition with the ground or footwear. However the attrition of the skin itself between the two faces of the interdigital space, mainly in their most proximal portion, may cause hyperkeratosis, often with secondary tissue maceration and infection, resulting in intertriginous callus.

Many terms to describe calluses have been used: hard callus, heloma durum, clavus durum, and hard corn mainly refer to callosities out of the interdigital space, such as the dorsum toe callosities or lateral callosity of the fifth toe. Soft callus, heloma molle, clavus molle, mirror corn, kissing corn, and soft corn describe interdigital callosities. The intertriginous callus can be mistaken for soft corn, being more precisely termed in English web-space corn. Currently we avoid using the Greek or Latin terms and their difference regarding texture or consistency, since there is no histologic difference among these lesions [6].

Toe Calluses

Clinical Presentation Digital calluses are directly associated with the use of enclosed-toe shoes and joint deformities that occur in the toes. The bunion, or hallux valgus, is the most usual deformity that impairs the big toe. It is a progressive deformity that deviates and rotates the joint during its evolution, thus favoring the growth of a medial protrusion called a bunion. Both rotation and bunion develop contact and attrition points that can create painful calluses, mainly through the use of closed shoes (Fig. 70.19).

Diagnosis Orthopedic changes which will secondarily determine skin alterations are mostly determined by radiologic tests.

Treatment Conservative treatment of bunion is effective for most patients in controlling the related symptoms. Retractors, protective devices, night contention orthosis, footwear change, physical therapy treatment, and anti-inflammatory drugs can be used as alternatives or to postpone surgical procedure. Corrective surgery is indicated when the conservative

Fig. 70.19 Hallux valgus

treatment fails, the deformity progresses when assessed through serial radiologic tests, and when there is discomfort with or inability to wear appropriate shoes for sports or professional activities. Many techniques are available for surgical treatment.

Orthopedic Deformities in the Toes

Clinical Presentation The three more common deformities that impair the four smaller toes are mallet toe, hammer toe, and claw toe. Mallet toe is plantarflexion deformity of the distal interphalangeal joint. This change brings about the development of a dorsal callus, often painful, resulting from attrition by some part of the shoes and/or a callus on the toe tip that causes nail deformity through contact and direct ground impact. It is more often seen in the Index Minus foot and impairs mainly the second and/or third toe (Fig. 70.20).

Hammer toe is a deformity in the plantarflexion of the proximal interphalangeal joint. It may lead to a painful dorsal callus caused by contact with part of the shoes, although it may also result in a callus on the toe tip and nail deformity. It may
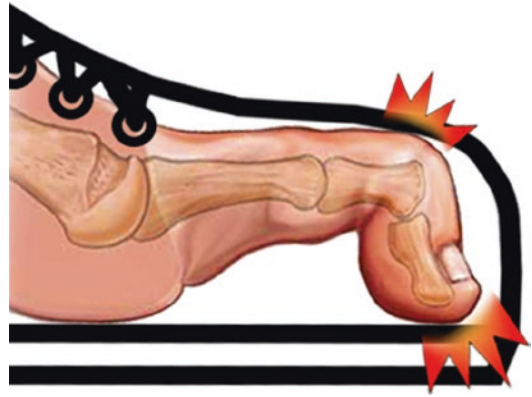
Fig. 70.20 Plantarflexion deformity of the distal interphalangeal joint
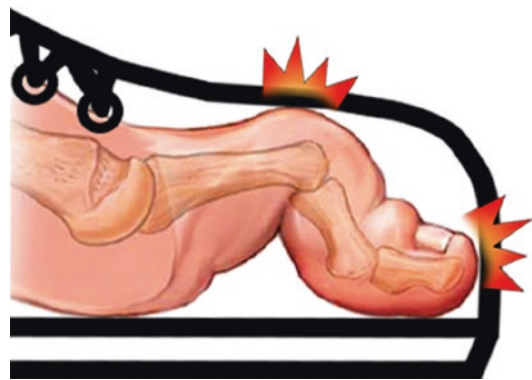
Fig. 70.21 Plantarflexion of the proximal interphalangeal joint

manifest as an isolated deformity or a multiple toe deformity (Fig. 70.21).

Lateral callus of the fifth toe results from attrition and pressure against the lateral edge of the shoe, and can be related to hammer deformity of this toe [6]. The pain can be extremely uncomfortable, mainly when pointed shoes are used (Fig. 70.22).

Claw toe is a more complex deformity and involves hyperextension of the metatarsophalangeal joint and plantarflexion of the proximal and distal interphalangeal joint. This alteration results in painful dorsal calluses and metatarsal pain due to the anterior displacement of the plantar fat pad. It usually impairs multiple toes and is associated with neuromuscular dysfunction (Fig. 70.23).

Fig. 70.22 Dorsal and lateral calluses of the fifth toe

Fig. 70.23 Claw toe

Fig. 70.24 Conservative method for alleviate symptoms
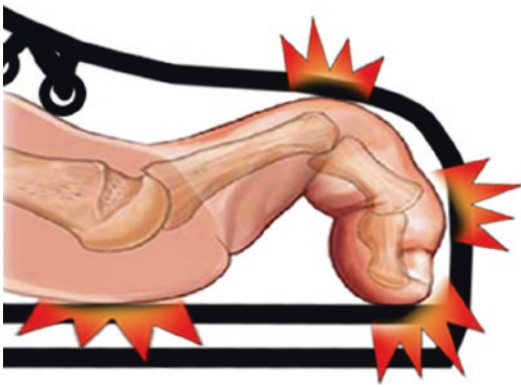
Diagnosis The study of the foot's morphological aspect and its radiologic investigation are the main methods of diagnosis.

Treatment All of these deformities are seen as a rigid or flexible configuration, and this can be assessed by an orthopedist who can better guide the method of treatment to be used. Footwear changes, contention devices, interdigital retractors, and silicone finger coats are conservative methods that may alleviate symptoms, although they do not correct deformities (Fig. 70.24) [7]. Surgical treatment aims at aligning and correcting toe deformities, establishing a more anatomic position, and avoiding footwear attrition and pressure points. There are many surgical techniques that can be used in isolation or in combination, depending on the deformity intensity, rigidity, and/or associated joint deviations. Osteotomies, condylectomies, arthrodeses, tendon transfers, and lengthenings are among the procedures used by the orthopedic surgeon to correct deformities of the smaller toes.

Interdigital Calluses

Clinical Presentation Interdigital calluses are hyperkeratoses resulting from skin contact and compression between two toes, precisely between two condyles, or between an ungual corner and the condylus, or even between joint osteophytes if there is arthrosis in the interphalangeal joints [8]. They have no relationship with direct attrition with footwear, although footwear compressing the feet laterally, mainly pointed shoes, plays

a role in lesion severity and increased pain. Often times they can be mistaken for fungal infections, mainly when lesions are deep and ulcerated [9]. These calluses can be called mirror calluses since both contact faces of the interdigital space display hyperkeratosis, and they are both painful (Figs. 70.25, 70.26, and 70.27).

Fig. 70.25 Skin contact and compression

Fig. 70.26 Mirror callus: deep ulcer

Fig. 70.27 Mirror callus: ulcer (see raised borders)

Treatment Conservative treatment of interdigital calluses aims at symptom alleviation and avoidance of skin ulceration. The use of rounded and larger shoes that provide space for all toes, the use of protective devices or interdigital retractors, and the elimination of local hyperkeratosis growth provide better comfort and prevent worsening of the lesions (Fig. 70.28). There is an indication of surgical treatment if the conservative treatment fails or provides no adaptation, or if the ulcerated lesions display difficult resolution or feet deformities. Joint realignment through resection osteotomies or condylectomies are the main goal of the surgical techniques used to correct interdigital calluses.

Intertriginous Callus

Clinical Presentation Intertriginous callus is observed in the most proximal portion of the interdigital space, mainly between the fourth and fifth toes, and less frequently between the third and fourth toes. Different from the interdigital callus, the hyperkeratosis of the deepest portion of the third or fourth space results from attrition of the skin faces and folds, which entails tissue maceration and fissure. Fungal infection is usually present, favored by the ongoing presence of a humid space and abundant scaling tissue (Fig. 70.29). The association of mechanical hyperkeratosis and tissue mycotic infection promotes lesion deepening at the subcutaneous

Fig. 70.28   Protective devices

Fig. 70.29   Intertriginous callus and fungal infection

plane, and a fistula track develops that maintains lesion chronicity and leads to bacterial secondary infection (Fig. 70.30).

Diagnosis The clinical presentation helps the diagnosis. Microbiological tests confirm secondary infections.

Treatment Conservative treatment is based on the use of interdigital protective devices, such as foam, gauze, or cotton pads. Drying, antibacterial, and antifungal agents can be useful. The surgical treatment of the intertriginous callus must focus on debridement and local tissue correction. Syndactylization provides interdigital space closure and tissue regularization. Besides correcting and closing the space via a skin plastic procedure, an osteotomy of the condyles of the base of the involved proximal phalanx may be necessary (Figs. 70.31, 70.32, and 70.33) [10].

Fig. 70.30   Intertriginous callus and bacterial infection

Fig. 70.31   Resection of the intertriginous callus

Fig. 70.32 Suture of the fourth space syndactylization

Fig. 70.33 One year after syndactylization

Callosities (Tylomas)

Callosities or tylomas are hyperkeratitic reactive lesions, larger than calluses. They can be seen in areas of more friction and pressure, encompassing a broader area, with more attenuated edges and showing more diffuse painful symptoms.

They are usually related to postural changes of the gait or more complex anatomic alterations of the feet.

Deformities involving more than one metatarsal bone, with no protrusions or specific contact or attrition points, may develop larger areas of plantar hyperkeratosis [11].

The mechanical or anatomic failure of the first ray is an alteration leading to development of diffuse plantar callosities. Deformity evolution in the hallux valgus (bunion) may lead to head support failure of the first ray, thus transferring a

Fig. 70.34 Callosities: deformities and large area of plantar hyperkeratosis

great amount of the foot's frontal support to the lateral metatarsal heads (second, third, and fourth metatarsal bones). Likewise, surgical procedures to shorten or cause joint instability of the hallux unbalance the distribution of the plantar support load and transfer it to the other rays (Fig. 70.34) [11].

Postural changes affecting the foot and the gait may result from many conditions. The most usually associated conditions include genetic deformities, such as idiopathic cavus foot, congenital crooked foot, and tendon shortening; neurologic disorders, such as cerebral palsy, spina bifida, myelomeningocele, poliomyelitis, and Charcot-Marie-Tooth syndrome; and trauma sequelae, such as rachimedullary trauma, peripheral nerve lesion, and severe foot fractures or burns [12].

In postural changes of gait, callosities usually develop through a mechanism of plantar overload in the anterior portion of the foot. The shortened posterior muscle of the leg (gastrocnemius) or the calcaneus tendon (Achilles) continually pushes the frontal portion of the foot against the ground at each step, thus stressing pressure under the metatarsal heads.

Cavus foot (Fig. 70.35) and equine foot (Fig. 70.36) deformities limit the unloading areas and concentrate the body weight on smaller support surfaces, significantly increasing pressure on the plantar regions in contact with the ground.

Diagnosis The clinical and radiologic presentations are important for diagnostic definition.

Treatment Conservative treatment for plantar callosities aims at providing symptom improvement and comfort when standing or deambulating, with relief of critical support and pressure points. Patients with mild deformities and mild or less symptomatic callosities are encouraged to change footwear and try more anatomic and comfortable footwear models, with more appropriately comfortable insoles, which may be enough for symptom improvement. Motor physical therapy aiming at stretching, reinforcement, and proprioception enhancement play an important role for patients with muscular imbalances and/or tendon shortening [13]. Hyperkeratosis surface debridement with a scalpel must be conducted by skilled professionals and carefully carried out, without invading the deepest skin layers. Unloading and adaptive insoles may be prescribed for pressure point relief and avoidance of early development of a new hyperkeratotic zone. Keratolytic creams and lotions based on salicylic acid can be used as ancillary agents to treat plantar callosities [14]. The use of orthoses and special footwear acts by adapting more significant deformities, protecting

contact and attrition points and balancing possible length discrepancies of the lower limbs. Surgical treatment aims at correcting the current deformities, thus restoring a more anatomically and physiologically possible plantigrade posture. Balance and plantar pressure distribution restoration, provision of appropriate footwear, and even modification of the ability for physical and labor activities are possibly achievable goals [15]. The most significant factor in surgical treatment is the correct choice of the various techniques which can be used for the different types and grades of deformities. Identification and understanding of the primary pathology, as well as the specific aspects of each deformity, are central to foreseeing the reaction and outcome of the indicated surgical treatment [16].

Plantar Wart

Concepts Among the most often seen skin lesions, warts are mainly diagnosed in children, and also affect about 7–10% of the population [17]. A wart is a benign proliferative epithelial lesion that results from infection by the human papillomavirus (HPV). There are many HPV subtypes that account for different clinical presentations of wart, and they also impair different body parts. Both plantar wart and palmar wart result from infection by type 1 and 2 HPV.

Clinical Presentation Plantar warts can manifest according to various impairment patterns, from single small lesions (1–2 mm) to multiple large lesions making up a mosaic of small hyperkeratotic papules (Figs. 70.37 and 70.38). Because this kind of wart impairs the foot sole in areas of constant pressure or contact, it prevents the spontaneous protrusion of the proliferative hyperkeratotic tissue. It thus results in increased intradermal tissue with a significant local compressive effect and an extremely painful lesion.

Diagnosis The most often used method for the diagnosis of plantar warts is the identification of capillary papillae or crests, small intralesional red, brown, or black points. It is sometimes necessary

Fig. 70.37 Plantar wart

Fig. 70.38 Mosaic pattern of plantar warts

to thin out the wart surface layer with a scalpel for a better visualization of these bleeding points [18]. Dermatoscopy can be successfully used in most cases. Before starting a plantar wart treatment it is worth informing the patient that many warts spontaneously disappear, mainly in children. About 50% of all warts in children disappear within 2 years with no therapy.

Treatment Many methods have been described, mostly through tissue ablation of lesions. The HPV virus is an aggressive intracellular virus, and tissue destruction is the most effective method to eliminate the virus. Treatments to destroy and eliminate the infected tissue include cold cauterization (cryotherapy), heat cauterization (electro-cauterization), and cauterization with chemical substances (chemical ablation) [18]. One of the

most frequently used treatments for plantar warts is cryotherapy with liquid nitrogen [19]. The lesion has to be deeply thinned out with a number 15 scalpel, followed by two applications of 10 s each, with a 10-s break between each application. Phlyctenae can develop after the applications, and drainage is allowed only when the warts are painful. Wound dressing has to be closed with gauze and antibiotic ointment. The application may be repeated monthly for 2–3 months. In case of numerous or recurring lesions, many topical therapies have been reported as effective [20]. Chemical ablations with phenol, 10% formaldehyde, and 10% formaldehyde with monochloroacetic acid and bleomycin sulfate are described [21, 22]. Topical treatments with cantharidin, salicylic acid, and podophyllotoxin may be applied either in isolation or combined [23, 24]. The use of topical five-fluorouracil, combined or not with salicylic acid, is also described [25]. The pulsed dye laser is also regarded as effective for treating plantar warts [26]. Electrical cauterization or carbon dioxide laser (CO_2) are not recommended, since they can bring about clouds of smoke wherein virus particles may be present [27].

Glossary

Bunion A bony bump that forms on the joint at the base of the big toe. A bunion forms when the big toe pushes against the next toe, forcing the joint of the big toe to get bigger and stick out.

Bursitis Inflammation and swelling of a bursa. A bursa is a fluid-filled sac which forms under the skin, usually over the joints, and acts as a cushion between the tendons and bones.

Condylectomy Excision of a condyle. Plantar condylectomy has been presented as a procedure indicated in the correction of dislocated metatarsophalangeal joints.

Eccrine poroma A benign adnexal neoplasm composed of epithelial cells that show tubular (usually distal ductal) differentiation, derived from sweat glands.

Keratodermia Any skin disorder consisting of a growth that appears horny.

Osteophytes Bony projections that form along joint margins, commonly referred to as bone spurs.

Osteotomy A surgical operation whereby a bone is cut to shorten or lengthen it or to change its alignment.

Paresthesia A sensation of tingling, tickling, pricking, or burning of a person's skin with no apparent physical cause.

Synovitis Inflammation of a synovial (joint-lining) membrane, usually painful, particularly on motion, and characterized by swelling, due to effusion (fluid collection) in a synovial sac.

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Multidisciplinary Team and Dermatological Care

Dermatologic Assistance in Primary Health Care: A Nursing Approach

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Key Points Summary
- A skin lesion is a public health problem and should be addressed by health professionals within primary health care.
- Considering the increase of the elderly population and the population's life expectancy, the burden of chronic diseases in Brazil is increasing, requiring a new healthcare model, particularly for noncommunicable diseases, classified as cardiovascular diseases, cancer, diabetes, and chronic respiratory diseases.
- The organization of nursing professionals in caring for people with lesions is a challenge because it is characterized by an approach of various dimensions with the establishment of various relationships, and is dependent on user coparticipation.

Introduction

In the past 30 years an increasing number of countries have sought to qualify the concept of primary health care (PHC) or, as it is called in Brazil, basic health care (BHC),[1] to incorporate the principles of sanitary reform. The Brazilian National Health System, Sistema Único de Saúde (SUS), adopted a new care model that seeks to incorporate the concepts of universality and integrality. BHC is developed within this system to be the first contact of the users with health care and to be the site responsible for the organization

[1] Although they have distinct meanings and epistemological origins, both expressions ("primary" and "basic") will be used in this text, as synonyms, given that, to the subject in question, do not apply the discussion about technological density, cost and nature of the procedure. In this case, it is an act of care that is listed on the scope of practices of the primary health care policy of the Brazilian National Health System and is not developed in all teams, involving matters related to the training of professionals and insufficient technical and material resources, as discussed below.

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of the health care of individuals, their families, and the population over their lifetime [1] and for their transfer between the different services that are required to solve their health demands.

The age structure in Brazil is changing very quickly, with the proportion of children and young people decreasing and the proportion of older people and their life expectancy increasing. These changes are quickly creating an age pyramid similar to that of European countries [2]. Analyses of the demographic transition in Brazil indicate that the speed of this transformation has been much faster than in those countries, reaching a growth of the elderly population with an acceleration five times bigger [3]. These changes bring challenges for all areas, imposing the need to rethink the extent of the supply of health services needed for the next decades. It is important to realize that this acute change not only affects public policy, but also the culture, family dynamics, and professional qualifications.

Considering the increase in the elderly population and the population's life expectancy, the burden of chronic diseases in the country is increasing, requiring a new healthcare model, particularly for noncommunicable diseases (NCDs), classified as cardiovascular diseases, cancer, diabetes, and chronic respiratory diseases.

Essential components [4] of the surveillance of NCDs are the monitoring of risk factors; the monitoring of morbidity and specific mortality of the diseases; the response of health systems including management, policies, plans, infrastructure, human resources; and access to essential health services and pharmaceutical care.

By 2022 Brazil [2] will have a population of approximately 209.4 million people and follow a growth course whereby it will reach a ratio of 76.5 elderly for every 100 young people. In this perspective, NCDs will remain at 45.9% of the global burden of disease; in other words, scores will remain similar to the current ones, but with a substantial increase in the number of elderly and onsets, so that today for every three adults in the world one has hypertension, and for every ten, one has diabetes.

Dermatologic nursing care is the theme to be addressed in this chapter, and therefore it is

essential to establish the situation to show that this is a public health problem that must be faced by health professionals in the field of primary care (PC). In this context, the nurse, as a member of the multidisciplinary team both in the traditional basic units and in the Health of the Family Teams, effectively acts with education for health, prevention, evaluation, and skin care. According to the National Primary Care Policy (NPCP) of the Brazilian National Health System, PC is developed with a high degree of decentralization and capillarity, and close to the places where people live and work. For care in the SUS, this mode of attention should be the chosen contact of users, the main entrance, the place where most of the problems that affect the population of the area are solved, and the communication center of the entire health care network [5]. Thus, there is a double insertion of the question of skin issues in the nursing routine and the same for other members of the primary care team: the care itself and the management of the user transfer between all necessary services.

Based on the discussions presented, the objective is to discuss and stimulate reflections about the importance of the nurse professional in the care of a patient with skin lesions, emphasizing PHC as a resolute point of attention and the basis for the management flow in the field of skin care.

Figure 71.1 presents the characterization of Brazilian PHC.

Nursing Practice in Skin Care

Cutaneous conditions are responsible for a significant portion of care provided in the diverse health services, regardless of the type of service, basic health units, ambulatory services, or hospital stay. Nursing constantly is faced with people suffering from wounds that are difficult to heal and who have a history of constantly searching for services for skin care. In the scenario of most health facilities in urban centers, as well as people who visit health services there also exists the problem of bedridden people originating from anticipated hospital discharges or even incapacitating chronic diseases. A thorough evaluation is
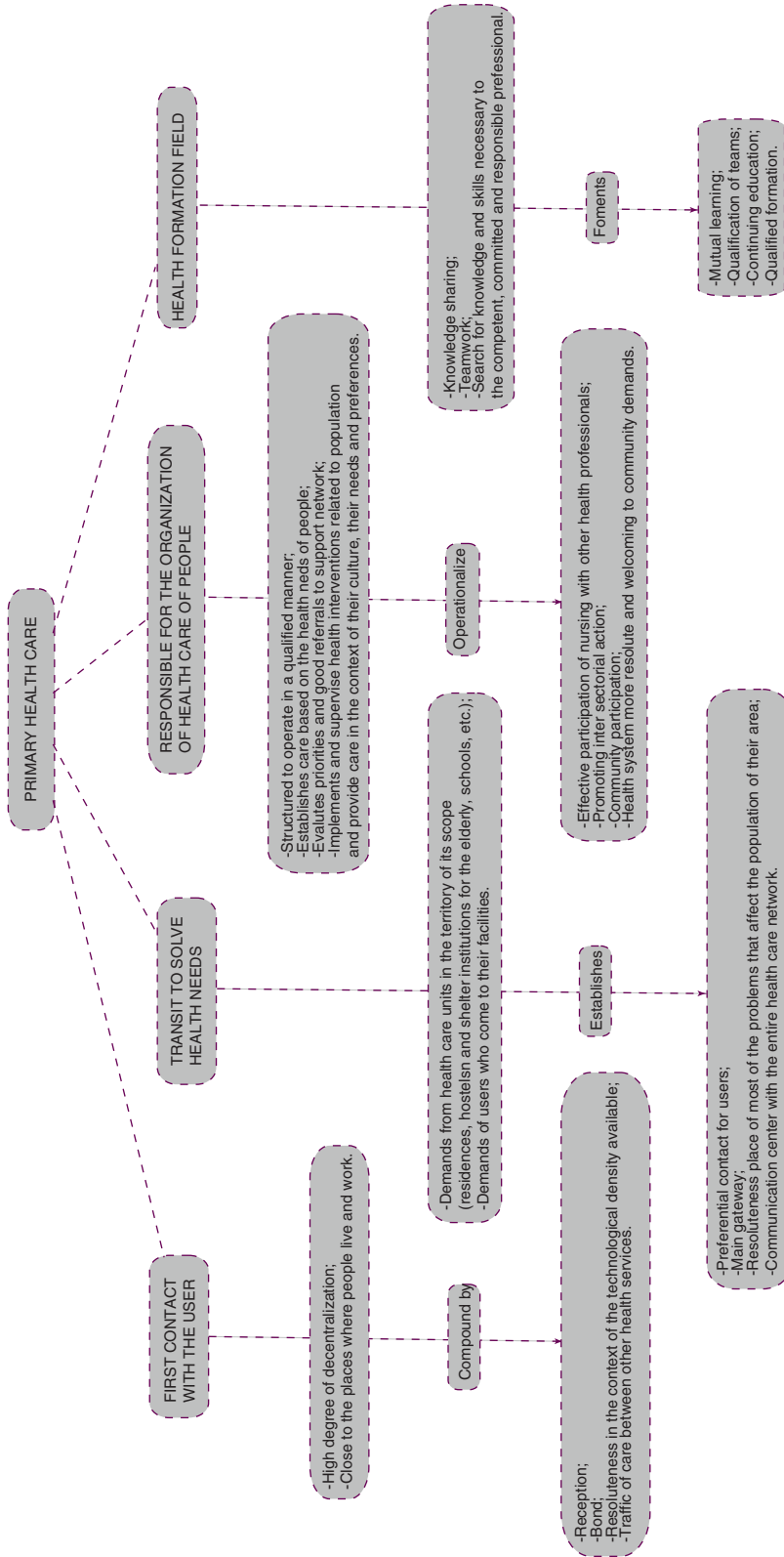
Fig. 71.1 Characterization of Brazilian primary health care

necessary to find important facts that will collate the targeting and the effectiveness of actions to be developed, creating the need for updating of knowledge properly linked to the care of wounds, either in specialized services or by professionals for referral to more specific consultancies.

In Brazil, wound care has always been an everyday activity in nursing practice, and therefore has been designed as a theoretical and scientific framework capable of mediating the complex associations of the needs required by the person with skin lesions. Such practices have enabled the enlargement of a significant knowledge base, consolidated in many manuals and institutional protocols in this field. However, the existence of care capacity for these problems tends to be concentrated in referral services and hospitals.

In this world of complexity, the Health Care Network (HCN) [1], which integrates the SUS, has sought to ensure universal, full, and free access for the entire population. It should be clarified that these are organizational arrangements of health programs and services, which have different technological densities and are integrated through technical, logistical, and managerial support systems in order to guarantee the integrality of care.

These networks can be hybrid productive arrangements that combine the concentration of certain services with the dispersion of others. In general, lower density technology services such as the BHC must be dispersed; on the contrary, the highest technological content services such as hospitals, processing units for clinical pathology tests, imaging equipment, and so forth, tend to be concentrated [1]. Here a critical question concerns the need for access to materials and specialized support in primary care to ensure resolute service.

Care is considered as the object and the essence of nursing, an affective knowledge that relates to distinctive acts. Dermatologic interventions performed by nurses are characterized as care when certain behaviors of care are added, such as respect, kindness, attention, solidarity, and interest [6].

Considering the need for integral and multidisciplinary approach to care for the person with skin lesions, the need to reflect on the organization of the networks, but also aspects of micropolitics of work that are developed in these environments to ensure proper and resolute care of these demands should be emphasized.

Operationally, the HCN consists of five components [1]: the communication center, the primary health care; the sites of attention to secondary and tertiary health care; the diagnostic and therapeutic support systems, the pharmaceutical care, the telemedicine, and the health information systems; the logistics systems such as electronic records on health, access systems regulated to care and health transport systems; and the governance system of the HCN.

The network supports sites of attention designed to ensure the commitment to the health of the population in a horizontal association, in other words, nonhierarchical between different sites, offering continuous service within the different levels of health care. Thus, in the care of people with dermatologic issues, a health unit, with intermediate technological density, but with the ability to operate with lightweight technologies [7], is also important when ensuring the guarantee of health to the person with skin lesions as a center of specialties with different multiprofessional teams, because both of them comply with distinct and important roles to specific and resolute needs. Primary health care usually takes demands from sites of attention in the territory of its scope (residences, hostels and shelter institutions for the elderly, schools, etc.) and users that arrive at their facilities. The importance of lightweight-type technologies (relational) is in the production of user embracement, the bond between patient and health professional, and resoluteness in the context of the technological density available. Equally important is the work mobilized for this type of technology to organize the transit of care through other services.

Considering that primary health care needs to be structured to operate in a qualified manner, resoluteness in skin care requires to be effective in the health unit, reducing the demands for specialized services or avoiding hospital admissions, that usually are responsible for inappropriate overcrowding of the system. For example, a

repressed demand in specialty areas such as angiology means that the assessment and the systemic and multidisciplinary approach occur at a time when the lesions are already extant [8]. By contrast, a fragmented organization of the network in dermatology leads to a disorganized work approach in the sites of attention: if the care takes place via an isolated and incommunicable approach between services, everyone will be incapable of paying continuous and effective attention to this population [1], with social, sanitary, and political consequences. The reason for the health care network is the population placed under its health responsibility, precisely the needs of its users. This reinforces the concept of a network with flexible, articulated, and integrated design, which communicate with different levels of technological density from the services, thereby facilitating access for people with skin lesions and the care realized by nurses in different sites of attention.

The interventions of dermatologic nursing should consider multiple aspects, including sociodemographic factors, such as gender, age, level of education, marital status, income and occupation, as these will define the language of approach, the need of social support, and the capacity of sharing involvement in the prevention of complications [8].

From this point of view, dermatologic nursing is an extremely broad specialty, having no limits of age or types of lesion. The person with a skin lesion lives in singular sanitary territories, coexists socially with family and neighbors, and is registered and classified into subpopulations according to social and health risks. Children, adolescents, adults, or the elderly are in need of care that can be clinical, surgical, aesthetic, or psychological. The profound knowledge of the user population by nursing professionals is the basic element which makes it possible to obviate care only based on demand and to establish care centered on health needs, setting priorities and good referrals to the support network. This is a core of knowledge that includes care (preventive and curative aspects, involving the disease, any comorbidities, and risks) and management

(access to greater technological density services, supplies, and support resources).

Figure 71.2, presented below, details the nurse's performance in different sites of attention.

The involvement of the authors with a situation in academic practice, about a woman who had a skin lesion in the lower limb, raised an in-depth study and the creation of a clinical case with an interdisciplinary perspective to be discussed institutionally. It attributed a fictitious name to the woman, Mary, and the other actors involved. The story is presented in its full version in order to transport the reader to the center of this reflection and questioning, from the life experience of the authors in practice that occurred in 2015, setting a path for the teaching and learning of skin care:

Mary, Caucasian, 66 years old, married and mother of three daughters, is a housewife, and follows Evangelical Christianity. Since long ago, 1971, has a skin lesion on the dorsum of the right foot and therefore receives material from the Basic Health Unit (BHU) to execute the skin dressing at home. Nurse Claudia, from Forest BHU, routinely performs Home Visit (HV) at the residence of Mary to assess the need to receive the dressing material provided monthly by the Unit. Her family owns the land where Mary lives; there are three houses there. She lives in the house at the back with John (77 years old), her husband, and Celia (44 years old), who is her eldest daughter. In the house next to Mary's place lives her middle child, named Rita (43 years old), who is married to Jaime (54 years old) and has a 21 year old son, Daniel. The youngest daughter, Joana (41 years old), lives in front of the house. The husband of Mary is retired, but does some freelance jobs. He has a good relationship with Mary and appears to be who most accept the nurse's assistance in the search for help for his wife. However, he is very passive in the situation. Celia, the eldest daughter, is single and has as an occupation the distribution of publicity flyers. She is quite aggressive with health professionals who perform the HV and complains all the time that she has taken care of the mother's skin lesion for 40 years already, and claims that she never had the chance to get married because of this. Insistently refers when the team from the BHU visits that advances are not necessary, because she will not let anyone execute the skin dressing on her mother's foot anymore. For Celia, the skin lesion of Mary only gets worse after treatment performed in the HV. Also prohibits the mother to seek help or
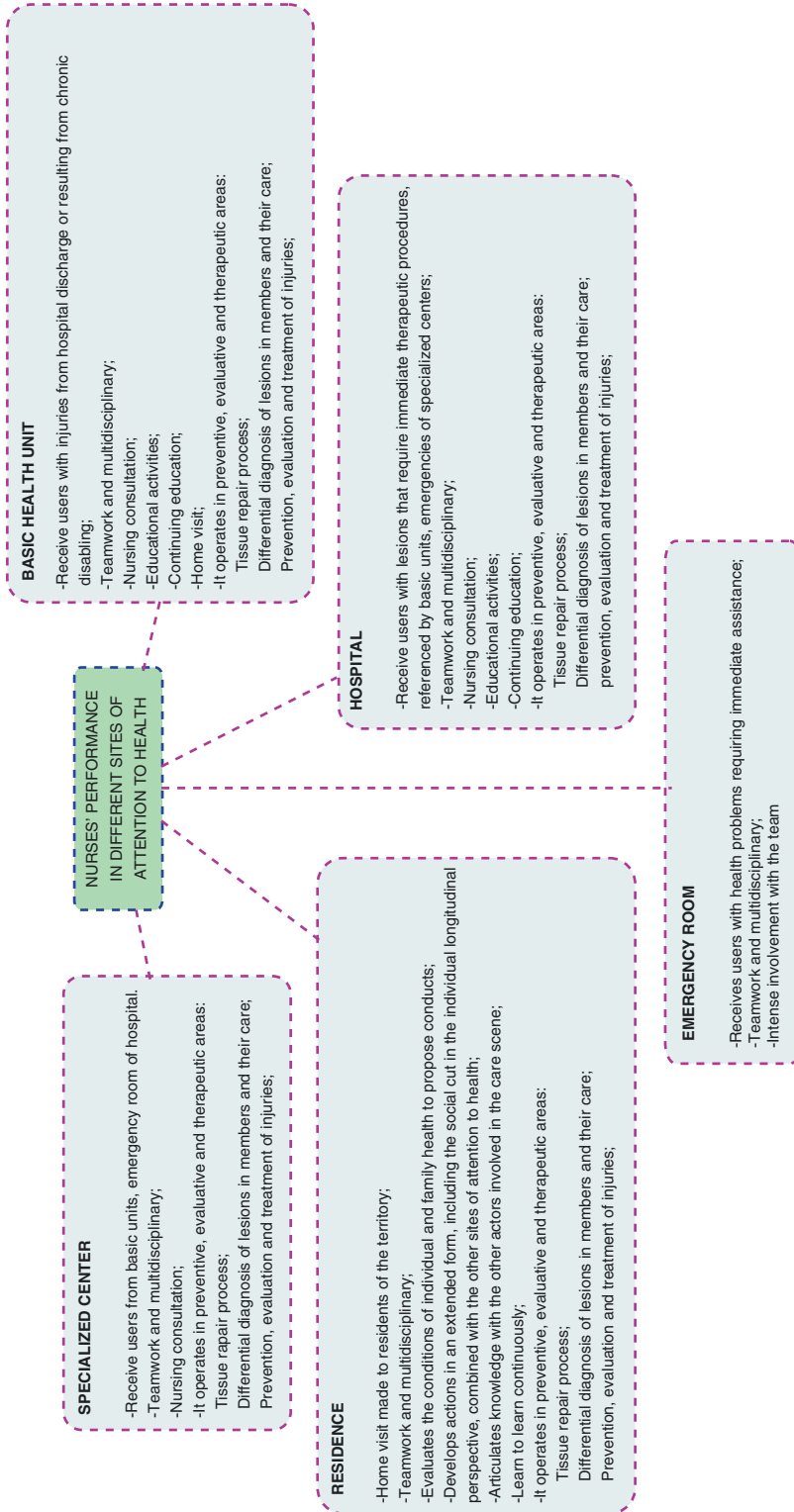
Fig. 71.2 Nurses' performance in different sites of attention to health

make the dressing with this team or any other healthcare service. Rita, the middle child, is married to Jaime, which is retired and has a chronic renal disease, currently waiting for a kidney transplant. Her son, Daniel, does not study and does not work. The couple is in a court fight with Rita's parents, Mary and John, claiming ownership of the house in which they live. They fight continuously with Rita's parents and sisters, complaining that they bullied Jaime, identifying him as wanderer and not as a chronic patient. To block the view by other family members a large yellow canvas covers their house and car. Daniel records with his cellphone the fights they have inside the family, and especially with Rita's younger sister, who spends the day listening to very loud radio. In one of the nurse's visits he showed the recordings that contain shouting and verbal abuse made between family members. Rita makes verbal complaints to the nurse in the presence of her father and mother, claiming that his father ordered him a friend Jaime's death. The youngest daughter, Joana, has lived in the front house for 20 years and remains isolated there without seeing members from her family or anyone else. Her parents provide food to her by the door window. All day long it is possible to hear very loud radio songs coming from Joana's house. Joana also records on her cellphone the fights with her sister Rita, Jaime, and Daniel. In mid-2013 there was a complaint to the prosecutor about Joana's state of health and since then she has been served by the Mental Health Team, with a diagnosis of possible schizophrenia. In one of the HVs, nurse Claudia found through the prescriptions provided by Joana's father that a psychiatrist of the Mental Health Team had accompanied her. In an attempt from the health professionals to approach the family was informed by one of the nursing staff from the Mental Health unit that Joana goes to medical appointments with her father wrapped in a cloth that hides her face. On the ground of the three houses, just in front of Mary's house, there is a lot of garbage accumulated. In one of the HVs, nurse Claudia found Mary in the courtyard, when approaching, Mary did not hesitate to kick, with the injured leg, a dead rat that was on the way to the door of her house. About her skin lesion, Mary knows little and shows no interest in seeking a Specialized Service to carry out treatment, although she is currently in the process to obtain retirement from the INSS because of her injury. At this visit she expressed that it would be a good time to get help and allowed the nurse to photograph the wound and carry out the skin dressing. On the last visit, despite the daughter Celia saying by phone that would not receive the BHU team, the nurse insisted and managed to see the wound, but not execute the skin dressing. Celia as well reminded the nurse that she should not come again

and that she had already said so over the phone. The nurse responded that she had brought the dressing material to deliver to Mary and she was there either to evaluate the wound and the need to continue delivering materials. The daughter asked to just leave the material, but the nurse insisted that without seeing and evaluating the wound she was not going to leave the material and could likewise cancel the request of material. This information triggered discomfort in Mary who then allowed the dressing change; the wound was had the same appearance as ever. It was agreed with Mary and Celia that care for the wound with guidance made by the nurse would take place at a new HV set for the next week to reassess the injury and execute a new dressing change, leaving for the moment the materials with the family. About 30 minutes after the return of the nurse to the BHU, Celia came with different clothes, saying that the BHU team were no longer allowed the visit her mother. Again she was told that the dressing material would be suspended, but if they needed help they could seek the BHU to talk. Facing this, the nurse...

This learning situation becomes a unique opportunity to resume and increase the interdisciplinary care concepts and their applicability in the daily practice of nurses. To attend a woman with a skin lesion, the consequences of which strongly affect her body, whose signs reveal her pain and deserve special consideration, ensures we are facing a unique story while at the same time resembling so many other experiences in the everyday care of people with skin lesions.

Thus, nursing care practices in the healthcare network gain significance, as it is in this field that many contexts express themselves clearly, reflected through the social and cultural approach to the population. Consequently, the health needs are identified on the spot, which can provide the development of more coherent and effective care practices [6].

Figure 71.3, below, shows the social and health inclusion of Mary and considers paths taken at different sites in the network's attention.

From the perspective of an articulated organization and inside a network, whose action can facilitate user access to different levels of complexity, the effective participation of nursing with other health professionals is essential, promoting intersectional actions that encourage community participation, seeking to make the health system
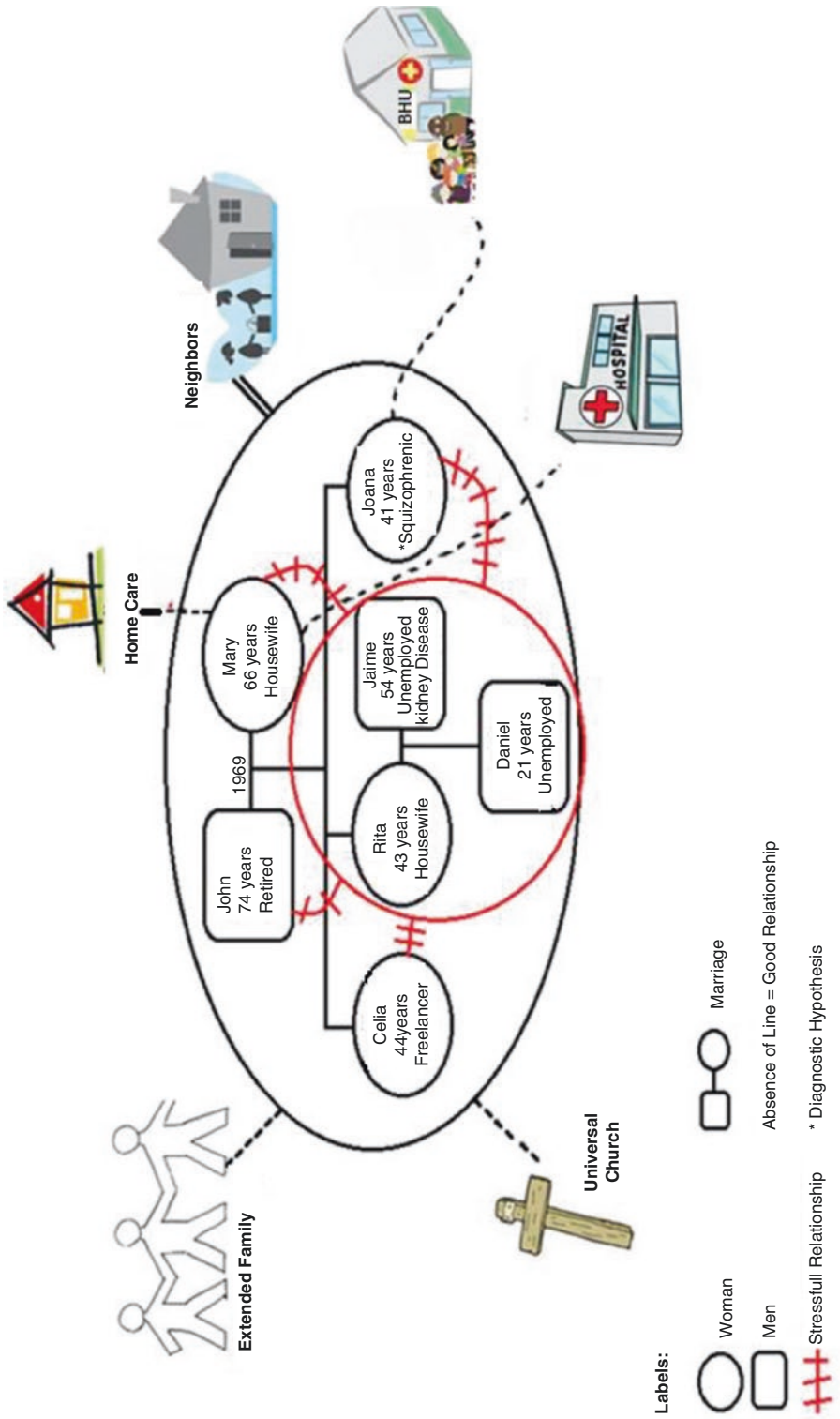
Fig. 71.3 Ecomap and genogram of Mary

more resolute, and welcoming to the demands of persons with skin lesions.

It is notable, however, that the organization of the work process by nurses requires consideration of the act of caring in terms of solidarity, with human relations, where flows of fondness happen between the professional and the user in a relationship of mutual responsibility to facilitate transfers inside the health care network [9]. It is also imperative to consider, and the case cited is plentiful in illustrating this, that care produces knowledge for everyone involved. In this case, a chronic skin lesion that does not react to the care procedures, it is stated that care is not always resolute and generates reactions in the group immediately surrounding the person requiring care. And these reactions, as well as those that permeate the way of life of the nuclear family and close relations with the user, make up the set of necessities that must be understood and managed by care professionals.

In the case of an articulated approach context among nursing, health professionals, and users, the organization of the processes that permeate the healthcare network can prove to be an excellent alliance. Nevertheless, the quality of care goes through many hands and implicates collective knowing and doing; in other words, there is a dependent association between all professionals [7]. Based on these considerations, it becomes a challenge to plan, implement, and evaluate the care for dermatologic health adopted or passed over, as the necessary interventions depend on the construction of interpersonal and professional relationships and the proper configuration of networks for care from the connections and linkages between the actors involved in the whole process. In the clinical case shown, the health needs related to comorbidity factors, besides the complexity of family relationships and territory, are also significant. There is no way to disregard the importance of the mastery of hard technologies (materials, supplies, and equipment) and moderately hard technologies (knowledge and protocols), but above all are the light technologies (relational) to congregate the health needs of people and to manage care [7] in situations of such complexity.

Therefore, the implementation and supervision of health interventions requires consideration of the risks to the population and the provision of care for people with dermatitis related to humidity, diabetic foot, vascular ulcers, myiasis, scabies, ostomy, minor burns, surgical dehiscence, abrasions and lacerations, bites, hanseniasis, pressure injury, skin tears, and care for the bedridden people in the context of their culture and their needs and preferences [1], considering also the existing resources.

The narrative that follows details another situation experienced by the authors, with the person called Emily, where although instigating reflections beyond the list of procedures, it also alerts for combined intervention strategies, fostering the creation of spaces built with life, motivation, confrontation, opportunities, and distinct social and collective contacts for nurses. This idea instills projective characteristics to the process of thinking and creating while retrieving desires, enabling new realities and new possibilities for the lives of those who live with the person with skin lesions.

Emily is 69 years old, black, currently single and Catholic, but believes in other religions. She has medical diagnosis of diabetes mellitus, hypertension, and anemia. For approximately 10 years she has had a venous ulcer on her left ankle, whose skin care was carried out in different services such as hospitals, ambulatory services, and specialized centers: a path guided by a precarious relationship with health professionals and short follow-up periods by these services. For example, in the Health Center, Emily disagreed with one of the vascular doctors from the service, and among comings and goings, decided to make the dressings by herself at home. In 2014, a teacher and her students met Emily in an academic activity of dispensing materials to affected users of skin lesions, and started to carry out home visits to assess the wound and execute dressing changes. After three months of follow-up, Emily agreed to consult with the nurse and the vascular doctor who supports the Basic Health Unit practice field of the group of students. In the same year she was diagnosed with uterine cancer that culminated in hysterectomy and radiotherapy. From this approach to the health service resulted the realization of a left saphenectomy at the hospital. After evaluation with the vascular surgeon, compressive treatment with an Unna boot was prescribed, with two changes per week, referring

*Emily to a specialized center. Emily has a singular life history. When she was born, her father left her in a boarding school. During childhood, she went through several internships and only by 13 years old could she live with her father. From this coexistence, she suffered maltreatment by her stepmother, which led her to seek the juvenile court because of the frequency of the attacks. At this time she was 15 years old. As a preventive conduct, Emily moved into the house of the judge that took care of her case and there she had to perform housework in exchange for shelter and food. After a while, feeling exploited, Emily asked to return to the boarding school, and then another family assumed responsibility for her and took her to live with them. Again, Emily was required to perform household functions. Over time she followed as a domestic, living in the houses. In 2015, she is retired with a minimum income and has difficulty in maintaining and caring for the skin lesion. Emily did not marry but had two daughters with whom she doesn't have a good relationship. Her daughters don't forgive her for putting them into boarding schools when they were small. Emily repeated her story with her daughters, not knowing another way of looking after her children and believing that leaving them in the boarding school was something normal. Emily has shown quiet courage and adherence to the treatment, which is distinctively reflected in her injury that has been progressing for epithelialization. In the latest assessment by the nurse in the Specialized Center, it was recorded: "**Subjective**: Emily mentions to be well and believes that the wound is getting better. Complains about some irritation under the left foot. She says that the wound pain reduced and so she is avoiding taking painkillers. Reports that she will miss this pain when it disappears and did not remember how it is to live without it. Inform that she takes many drugs because of her diseases. **Objective**: Ambulating with difficulty and with help of crutches. After examination of the skin it is possible to observe calluses on the plantar region of the left foot, one near the hallux and one on the first metatarsal head. Noted dirt on nails, suggestive of fungal colonization. Skin adjacent to the wound with ocher dermatitis. No signs of inflammation. Ulcer with granulation tissue. Intact and irregular edges. Serosanguinous exudate in small quantities. **Measurements**: 18.5 cm × 15.5 cm. **Interpretation**: Impaired Ambulation, Impaired Tissue Integrity, Risk of Infection, Chronic Pain. **Conduct**: Execute dressing in Ulcer of Left Lower Limb with Hydrofiber impregnated with silver and bandaging with Unna Boot. Retreat excess calluses on the foot with a scalpel blade. Hydrate lower limbs. Keep bandage two times a week. Analyze laboratory tests performed. Refer user to dermatologist."*

Fig. 71.4 Emily's wound: fabric with biofilm and fibrin. Macerated edges. Abundantly serous exudate, 2014

Fig. 71.5 Emily's wound: granulation tissue. Intact and irregular edges. Serosanguinous exudate in small quantities, in 2014

Figures 71.4, 71.5, and 71.6 show images of the evolution process of healing of Emily's Wound in the last 2 years of supervision.

Many situations, from both social as health systems, influenced this long and complex process of healing of Emily's wound, a complete and thorough medical history to evaluate all the factors that interfere in the healing of his wound having been fundamental.

Health has to be understood as an active condition against disease, linked to the state of being of the individual. For this reason it makes sense to ask Emily if she feels sick. To live with a skin lesion requires a redefinition of the confrontation

Fig. 71.6 Emily's wound: latest images, in 2015

to the constant visits to health services, the hospital admissions, laboratory and imaging examination, to the various evaluations of the skin lesion or dressing changes, not to mention the adverse effects such as pain, odor, discomfort, and therapy in their uniqueness, with the observation of all aspects in the process of becoming ill.

The care of the person with skin lesions is organized in a unique way in the relationship between the different sites of the network and health interventions, but a stable bond is necessary and it is desirable that this bond has been established in primary care. It is notable that the technical dimensions of care to people with wounds, being the main activities developed by the nurse such as the tissue repair process, the differential diagnosis of limb injuries and their care, prevention, evaluation, and treatment of skin lesions caused by pressure, or by neuropathy and angiopathy due to diabetes, and skin lesions can be performed in health care or in the user's home in a continuously and comprehensively routine manner. Therefore, the correct handling of the health conditions of the person with skin lesions has as one of its pillars support through self-care, which aims to prepare and empower people to manage by themselves their health and care [1]. All these situations are favored when the professionals have a good relationship with users and know their ways of life and the conditions under which they live and coexist.

The nurse's responsibility includes the important role of articulation of work organization to meet the needs of the users, integrating care activities with the skills and competence necessary for management and relational processes [9]. In complex cases, as health needs usually are, the ability to analyze the context and build therapeutic projects that transcend the logic of complaint-conduct that usually prevails when the professional uses only academic knowledge to take care of diseases (and not of a sick person) is essential. Therefore, home visits can be used as a care strategy, because besides planning the activity, assessing the conditions of individuals and family health to recommend conducts, the nursing professional develops enhanced mode of actions, including the individual cut in social longitudinal perspective, articulated with other network attention sites [6]. Given that no academic institution drains the supply of knowledge and technologies needed to care in the context of such complexity and to resolve this constant deficit, it is necessary to analyze, reflect, evaluate, seek new knowledge, and articulate knowledge with the other actors involved in the care scenario; in other words, it is necessary to learn continuously.

In the daily practice of nursing, care for people with skin lesions in different aspects of health care requires from the professionals the technical and scientific knowledge about nursing procedures, solutions, and techniques currently used to treat people with cutaneous conditions, seeking a way of care that it is not limited to the execution of dressing change but is also preventive and evaluative, accompanied by therapeutic activities through nursing consultations, home visits, and educational activities. An open attitude to continuing health education it also required [10], understood as the grounded learning on issues of daily work, where knowledge and user information about where he/she lives and circulates, the technical and scientific knowledge of the professional, the information on the network of care and the way of organizing services and the work inside them, besides the knowledge produced in relation with the user make up the inputs required for this method of learning.

Regarding the selection of the treatment for wounds, it must be considered that they are all different from each other, and the indication of

care must be driven by particular characteristics of each lesion, such as necrotic tissue versus viable tissue, infected versus uninfected, amount of exudate, and pain, among others; relating this information to some important points that influence the healing process, such as control of the underlying disease, nutritional aspects, emotional state, infections, medications, immobility, and educational care associated with the treatment [11]. Moreover, it is necessary to remember that wounds are dynamic and change their characteristics when healing, requiring new modes of conduct, including changing the choice of topical therapy used.

Figure 71.7 summarizes the practice of the nurse in the care of a person with a skin lesion.

The nursing consultation is a space favorable to the development of care practices with the skin, as it gives nurses the opportunity to hear demands, evaluate the physical health and psycho-emotional conditions, get to know deeply the person, and initiate guidance, with the understanding of this person's socio-emotional context and family relations. Thus, this space favors a method of care that comprises an attitude of establishing constitutive relations to care for the other, strengthening the bond between professional and user for the best therapeutic decision [6]. It is important to remember that relational technologies can be also an excellent organizer of care, making it possible for the professional to establish the best conduct and offer the most appropriate treatment plan, unique to that user.

The educational activities are an important practice of care of nurses in the health care network, given that they relate mainly to the guidelines provided by them to various social actors. Educational activities, individual and group, compound the actions of care. This action runs through health promotion, prevention and control of diseases, self-care, and also the technical guidelines on performing procedures in dermatologic care. They are held by individual and collective consultations, lectures, and discussion groups [6], allowing the person to choose the best action. Educational activities are also produced by situations whereby the context in which the users live and the health problems are mobilized

are discussed and analyzed, including reciprocal learning for users and professionals. It is not only the transfer of information, which normally shows very low efficiency, the object that organizes the work of health professionals to educational activities, but also the exchange of knowledge, since, in addition to the knowledge available to the professional, situations are able to produce knowledge and practices that are appropriate by all the actors involved.

Final Considerations

Encompassing a discussion of the challenges that nursing professionals face in the care of the person with skin lesions is not considered a simple task, because in this specific scenario these professionals occupy key areas in the organization of the HCN, in which collective spaces of care require dialogue and evaluation of collaborative behavior, solidarity, criticism, and inter-subjectivity, whereby the ability to perform an accurate dynamic situational reading of the context in which the health system belongs is a unique and singular moment. As mentioned earlier, it does not seem possible to encompass the complexity that involves the health needs of people with skin lesions if there are no spaces of exchange in each service and between services; permanent education in health is a device of instruction and production of networks when it mobilizes different professionals involved in the care.

The complexity in discussing the various knowledge and skills that involve care is very large, requiring extensive and broad capabilities with high cognitive density. In this line of thought, viable proposals that help nursing professionals to answer to the particulars that skin care requires becomes necessary, considering the various sites of attention that are mainstreaming in HCN. This operates by the need of these professionals to reflect their ways of being in work, together with the consolidation of critical and purposeful pedagogic spaces that allow one to visualize more clearly the impact of the full skin care and, by extension, to be able to

HOME VISIT
-It operates in team;
-Evaluates the individual and family health to propose conducts;
-Develops actions in an extended form, including the social cut in the individual
longitudinal perspective, combined with the other sites of attention to health;
-Articulates knowledge with the other actors involved in the care scene;
-Learn to learn continuously;
-Performs dressings;
-It operates in preventive, evaluative and therapeutic areas

NURSING CONSULTATION
-Space favorable to the development of skin care practices;
-Listen to demands;
-Evaluates the physical and psycho-enotional health conditions;
-Exchange knowledge;
-Understand the socio-emotional context and family interactions;
-Establishes the best conducts;
-Guides care;
-Balances techniques of care:
    Tissue repair process;
    Differential diagnosis of lesions in members and their care;
    Prevention, evaluation and treatment of injuries;

CONTINUING EDUCATION
-Learning based in the work everyday issues;
-Knowledge and information about where the user lives and circulates;
-Technical and scientific knowledge from the professional core;
-Information on the network care and how to organize
the network sites and the work inside it;
-Knowledge produced in relation to the user.

EDUCATIONAL ACTIVITIES
-Create actions of care;
-Guide various social actors;
-permeate health promotion, prevention and control of diseases;
-Permeate self-care;
-They are produced from situations of users;
-They are produced from health problems that mobilize
the service, being discussed and analyzed;
-Result in mutual learning for users and professionals.

MULTIDISCIPLINARY WORK
-Intense involvement with health professionals;
-Ethical, humanistic and social commitment to multidisciplinary work;
-Communication / Integration / Interaction / Innovation;
-Professionals from different fields work together and problematize care nuances;
-Consolidation of critical and propositional pedagogical spaces in the skin care;
-Qualification of care and of the network sites of attention.

SITES OF HEALTH CARE NETWORK
-Home, communities, basic units, specialized centers, clinics, imaging or clinical analysis laboratories,
pharmaceutical care, emergencies, hospitals;
-Organizational arrangements of health actions and services, with different technological densities,
that requires dialogue and valuation of collaborative behavior, solidarity, critical and inter-subjective;
-Single act - dynamic and accurate reading of the need for health care, contextualized inside the health system;
-The care for the person with skin lesion is organized in a unique way by the relationship
between the different sites of the network and health interventions;
-Integrality of care;
-The link between the sites of attention is essential to provide integrality of care
within reasonable standards of cost/ effectiveness;
-It is desirable that the bond with the user is established in primary health care;
-Specialist play a role as an inter counselor and promotes support for primary care.

**THE SINGULAR PRACTICE OF
THE NURSE IN THE SKIN CARE**

Fig. 71.7 The practice of the nurse in the care of a person with a skin lesion

build strategies and actions to promote the qualification of care and HCN.

There are many aspects of HCN, and all involve the reference and counter-reference relations. In this perspective the consolidation of referencing actions stands out, because if we do not have a consolidated network we have a veiled dispute of forces between tertiary, secondary, and primary health care. And underneath this confrontation of forces, gaps are created in the care of a person with skin lesions, leading to discontinuity in care, forcing the user to wander between different sites of the health care network. To enhance resoluteness it is mandatory to pursue the development of a good structure of communication between services, covering the uniqueness of the health services that must meet these users and strengthening the primary care. In this approach of approximation between network sites, nursing has an important interlocutory role to facilitate and qualify access to sites of SUS's attention, regardless of the level of complexity of the injury or disease that affects the person seeking care.

By contrast, a new viewpoint of nursing concerning integral care to persons with skin lesions is essential. It is necessary that the nursing professionals view themselves as protagonists of their strategies and actions, individual and collective, in the dermatologic care to be developed, participating in their formulation and execution. A leading role should be taken that highlights the participation of nurses in the care of the skin and included as assignment so they can expand, inside the services and institutions, their actions on the integral care of skin at every site of the HCN, from Basic Units of Health or Family Strategy, ambulatory services, emergencies, or specialized services, to hospitals or home care.

The care of the person with skin lesions in the network is recent and there are no experiences of large-scale or robust assessments. However, successful and local nursing practices in the care of users with skin lesions in different parts of the HCN can promote a more effective way for professionals to find ways and realize the challenges they face in daily life, with significant impact on the healthcare population. Since it is possible to produce effective care to the person with wounds, it may be able to mutually support nursing professionals and teams and produce synergetic effects in various sites that the network connects [12], enhancing benefits such as reduced cost of treatment, short-term improvements and more participatory logic in the execution of their actions and policies. In addition to the health, economic, and social impacts, effective and significant systemic action by the user also produces the feeling of good care and feeds a favorable conception of the health service and the work inside it, as can be seen in the reported cases.

By all of these considerations, it is recognized that the training of nurses in the care of people with lesions should be a challenge for the healthcare system, as it is characterized by an approach of various dimensions and in developing multidisciplinary care plans, with the establishment of various relationships that depend on user coparticipation. This will force changes, not only theoretical but also in practice. Here, we face a double challenge: to insert this topic in professional structures and to build learning capacity in daily work, as demonstrated at various times in this chapter. On the other hand, care is also a challenge for the person with the skin lesion, as this individual will only stabilize if he/she participates actively, in close collaboration with the health teams that follow its treatment. In such a way, both professionals and users should be supported in policies, programs, and management organizations capable of supporting this type of care. The process of treatment, recovery, and wound healing is much more consistent when the teamwork and self-responsibility of the person being cared for are strong.

Glossary

Health Network Care (HNC) The organizational arrangements of health actions and services of different technological densities, integrated through technical support systems, logistics, and management, which seek to ensure care with integrality.

National Primary Care Policy The result of the accumulated experience of several historical actors involved with the development and consolidation of the SUS, such as social movements, users, workers, and managers of the three levels of government (federal, state, and municipal) developed with a high degree of decentralization, capillarity, and closeness to people's lives.

Sistema Único de Saúde (SUS) *Unified Health System*, the name of the Brazilian National Health System.

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Care of Wounds: Dressings

72

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Key Points Summary

- Wound and wound care – definition and context
- Evaluation of wound and its relevance for diagnosis and treatment
- Possible findings following evaluation of a wound
- The edge of the wound
- Etiology: arterial, venous, mixed, neuropathic wounds
- Evaluation of wounds: acute, chronic, complex; depth; infection; wound healing; phases of healing; the wound bed
- Treatment of wounds/types of coverage: dressings, ointments, and oils
- For the successful treatment of wounds, a complete assessment by a multidisciplinary team is necessary, leading to a comprehensive care plan for treatment and long-term monitoring of patients

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Concepts

The word *care* means "to pay attention," "take care of," "be responsible for," and denotes a dynamic action, thought, reflection. Thus, care has a connotation of responsibility and zeal, and the interactive care process includes actions, attitudes, and behaviors that are based on scientific knowledge, experience, and professional intuition, using critical thinking as its main tool. These behaviors are performed for and together with the individual needing care in order to promote, maintain, and/or restore their dignity and wholeness.

Concern in caring for wounds is ancient. Many civilizations evaluated and treated with existing resources and achieved results satisfactory for that time. The Egyptian civilization lent greater prominence to scientific and technical creations that even empirically treated wounds. It was they who concluded that infected areas closure with debridement healed rapidly and also classified the types of skin lesions and detailed treatment of each. Hippocrates in 300 BC suggested treatment with local heat, ointments, and removal of necrotic material. However, wound care has evolved, and in the late nineteenth century arose the concept that wounds should be kept dry and treated with antimicrobial substances to prevent contamination and infection. In the 1950s the first studies of wound healing in a moist environment appeared [1–3].

For the successful treatment of wounds the patient should be assessed by a multidisciplinary team who should establish a comprehensive plan for the treatment and long-term follow-up of the affected person [4, 5]. The concept of the wound is shown in Box 72.1.

> **Box 72.1 Wound**
> Wound is a disruption of skin integrity caused by physical, chemical, or biological agent, may reach the epidermis, dermis, subcutaneous tissue, fascia, muscle tissue, bones, organ cavities, and any other body structure [6, 7].

Clinical Presentation

Structured evaluation with clinical history, physical examination, collection of material for biopsy, culture, and log data is important to make the differential diagnosis and define systemic and local treatment, ensuring the proper selection of techniques and products to be used.

The evaluation of the perilesional area and the border is as important as evaluation of the wound bed. The perilesional area is the area that surrounds or encircles the wound. Its size depends on the etiology and the degree of compromise, as well as on the location of the wound. This area of the skin is exposed to exudative action resulting from both the wound itself and the application of products [8] (Fig. 72.1).

Particular findings are possible following evaluation of a wound:

Ocher dermatitis: Occurs due to extravasation of red blood cells in the dermis along the deposit of hemosiderin in macrophages, and presents as signs resulting from the confluence of purpuric spots, punctate, with hyperpigmented regions (gray-brown appearance) (Fig. 72.2).

Fig. 72.1 Perilesional area with scaly skin (*arrow*)

Fig. 72.2 Venous wound with ocher dermatitis (*arrow*) in perilesional area

Eczema: Skin injury resulting from inflammation that begins with erythema and edema. Fluids may accumulate in small vesicles. The secretion of a serous fluid may favor the formation of crusts [9].

Lipodermatosclerosis: Characterized as the concomitant presence of hard edema and slight pitting (sclerosis), diffuse pigmentation (ocher dermatitis), superficial scar areas, absence of hair, and hypohidrosis.

Maceration: Softening of the surrounding skin due to excess drainage or contact with fluids on intact skin. It can occur due to improper treatment or increased exudate due to changes in wound tissue.

Erythema: Redness of the skin due to increased blood flow in superficial capillaries; the color may range from pink to bright red that disappears by digital pressure. It can be due to

irritation by exudate or substances resulting from covers and adhesives.

Excoriation: Superficial injury caused by trauma or skin erosion.

Scaling: Detachment of skin in scales resulting from local drying.

Itching: Can be due to drying of the skin in contact with chemicals [10].

The *edge of the wound* is its external limit. It may present as attached, detached, undermined, hyperkeratotic, or macerated.

- Edge bonded and flat: indicates good evolution of the wound.
- Detached: indicates the need to pack for healing.
- Undermined: worn, bumpy, lumpy, with friable tissue that may rupture spontaneously or by any friction.
- Maceration: softening of the surrounding skin due to excessive exudate or constant contact with fluids.
- Hyperkeratotic: when there is excessive production of keratin leading to thickening of the outermost layer of skin (stratum corneum and epidermis) forming hard whitish tissue, which is due to mechanical irritation or pressure, usually produced to protect the site [10].

Etiology

The most frequent chronic wounds are those with vascular or neuropathic origin. Vascular wounds can be of arterial or venous background.

Arterial wounds are the result of a chronic ischemic process. Usually the wound bed is not exudative; the surrounding skin is atrophic and has no hair. There are severe pain, numbness, and muscle stiffness due to lack of irrigation of the sensory nerves, as well low temperature in the extremities due to poor blood circulation in peripheral tissues. It represents 5% of vascular wounds [11].

Venous wound may occur from failure in the venous pump, valve incompetence or thrombophlebitis history, and chronic edema of the affected limb. The wound bed is red with presence of excessive exudate. It is usually superficial, multiple in number, and extensive in area. The surrounding skin shows changes such as atrophy, hyperpigmentation, and ocher-hardened cellulite. It accounts for 80–90% of extremity ulcers (Fig. 72.2).

Mixed wounds have venous and arterial components in the genesis of the process and for its treatment it is important to define the predominant factor [11].

Neuropathic wound is caused by peripheral neuropathy resulting from diseases such as leprosy, diabetes mellitus, or alcoholism. Many factors are associated with the development of neuropathic ulcers: altered skin sensation, continued unaware pressure, loss of autonomic fibers that are responsible for maintaining the sebaceous and sweat glands, allowing the inelastic skin and dryness, which may easily cause cracks and injuries [4, 5].

Etiologically, wounds can also be classified as:

- *Accidental or traumatic*: when it occurs unpredictably, being caused by sharp or, blunt objects, piercing, lacerating, inoculation of poisons, abrasions, crushing, bites, burns, and others.
- *Intentional or surgical*: when caused by a proposed therapeutic purpose.
- *Pathologic*: these are secondary injuries to a particular underlying disease (diabetes mellitus, hypertension, leprosy, gangrenous pyoderma, venous disease, arterial, oncologic, and others).
- *Iatrogenic*: inappropriate result from medical procedures or treatments.
- *External factors*: lesions that appears as a result of continuous pressure exerted by body weight, friction, shear, and moisture, such as pressure ulcers.

It is important to define the etiology of the wound because the treatment is an integrated and continuous process involving a multidisciplinary team [12]. In this connection, the reader is referred to the management chart that follows. Another important issue is to highlight the importance of the affected individual as a singular being who should not be addressed out of his/her familiar and
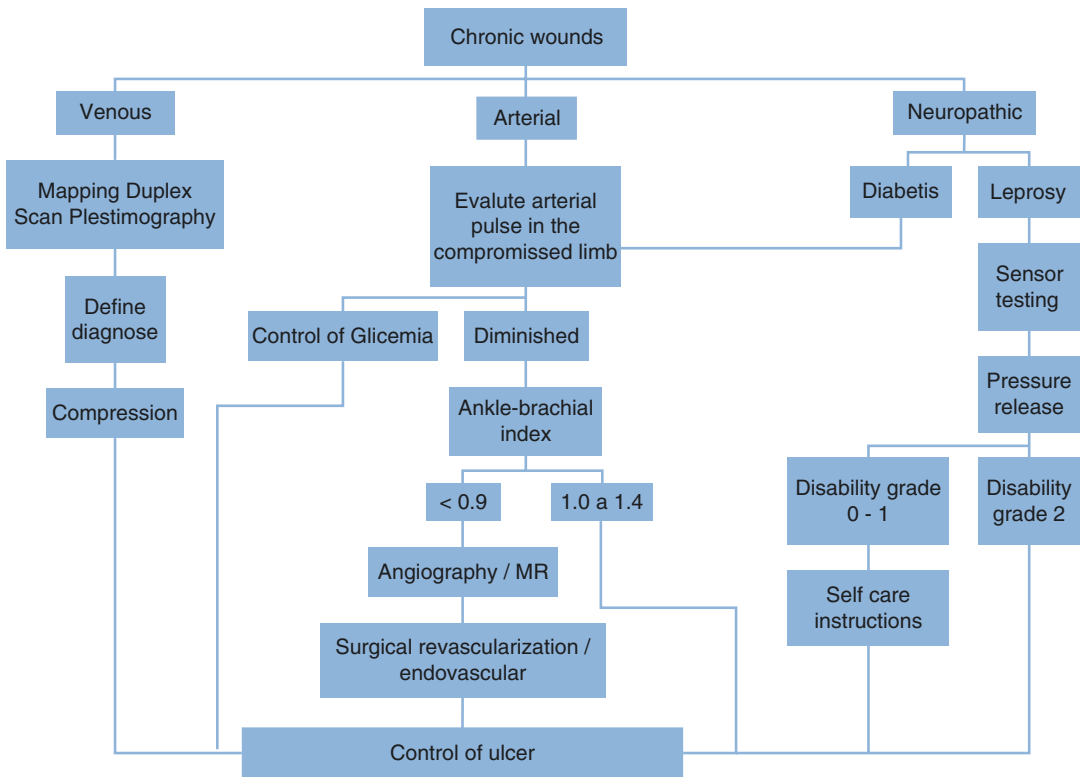
social context. As important as the etiology are the factors that slow the healing process, such as age, obesity, smoking, impaired nutrition, stress, anemia, hypertension, diabetes, and use of medications that interfere with coagulation, with platelet function, or in the immune responses [13].

Management Chart for Chronic Wounds

Diagnosis: Evaluation of Wounds

Taking into consideration the time span, wounds can be considered as acute and chronic.

*Acute wound*s originate from surgery or trauma, and repair occurs in a timely manner, without complications.

Chronic wounds are those that fail to progress through the orderly healing process, exceeding 3 months.

Complex wound is a new concept which aims to identify those chronic or acute wounds that are difficult to resolve using conventional and simple dressings. Complex wounds have high morbidity and mortality and have been identified as a serious public health problem in many centers, and must be approached by a multidisciplinary team [1, 14].

There are other aspects of the wound to be covered during the evaluation: depth, etiology, presence of infection, wound type, and phases of the healing process.

Depth

- Superficial: affects only the epidermis and dermis.
- Deep superficial: destroys the epidermis, the dermis, and the subcutaneous tissue (Fig. 72.3).
- Total deep: reaches the level of muscle tissue and adjacent structures.
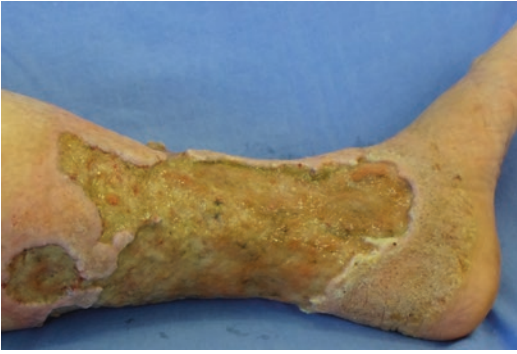
Fig. 72.3 Wound with superficial depth with silver impregnation points, indiscriminate use of silver coverage

Presence of Infection

- Clean or aseptic: free of pathogenic microorganisms; produced without glitches under aseptic conditions through an incision in sterile tissue or of easy decontamination, without evidence of signs of inflammation.
- Colonized or contaminated clean: the presence of microorganisms on its surface that proliferate due to a favorable environment, but do not trigger infection, which may or may not contribute to delay in the healing process. No obvious clinical manifestations.
- Contaminated: those recent accidental wounds that remain open for a period of time longer than 6 h and are invaded by considerable bacterial microbiota, although not virulent.
- Infected or septic: features over 100,000 colonies per gram of tissue or presenting an obvious infectious process, such as devitalized tissue, purulent exudate, and characteristic odor. They are potentially colonized by microorganisms such as parasites, bacteria, viruses, or fungi, due to reduced immune defenses.

An infection is the invasion and proliferation to deeper tissues layers of microorganisms from the wound bed, producing a reaction of the host as response of polymorphonuclear leukocytes causing local clinical symptoms (pain, heat, redness, odor, and purulent or seropurulent) and/or systemic (fever, loss of appetite, malaise).

The line that separates colonization and infection is not always clear, and in recent years the concept of bacterial load, defined as the concentration of microorganisms per gram of tissue of the wound, has been granted great importance.

The biofilm is a challenge in the treatment of chronic wounds. The biofilm is a community of microorganisms surrounded by a mucopolysaccharidic extracellular matrix creating a cohesive film in the wound bed that serves as a common defense strategy of these settler microorganisms.

Control of the biofilm is a fundamental part of the treatment of chronic wounds. Debridement, maintenance, and use of topical antimicrobials are more effective than systemic antibiotics. These should be reserved for the treatment of systemic infection (osteomyelitis, cellulitis, bacteremia, among others), because of the continuous increase of antimicrobial resistance to antibiotics [10, 11, 15].

Regarding the Type of Wound Healing

- First intention: occurs when the edges are rough, with minimal loss of tissue, absence of infection, and mild edema. Granulation tissue formation is not visible. Example: a surgical wound that is sutured.
- Second intention: occurs when there is excessive loss of tissue with the presence or absence of infection. The primary approximation of the edges is not possible. The wound is left open and closes by means of contraction and epithelialization.
- Third intention: occurs when there is an approximation of the wound edges (skin and subcutaneous) with suture after infection control and formation of granulation tissue, for better functional and aesthetic results.

Phases of the Healing Process [4]

- Hemostatic and inflammatory phase: vasoconstriction occurs shortly after the trauma; bleeding stops due to the presence of platelets; there are fibrin clots that activate the coagula-

tion cascade, resulting in the release of substances forming the provisional extracellular matrix. This matrix is the support for the migration of inflammatory cells, followed by activation of protection mechanisms and tissue preparation for the development of healing. The clinical manifestations are pain, heat, swelling, redness, and loss of function. These signals can be minimal, transient, or lasting.

- Intermediate or proliferative phase: includes granulation tissue (neoangiogenesis, proliferation and migration of fibroblasts, collagen synthesis) and epithelialization (maturation of the extracellular matrix consists of basic elements of the basal membrane, such as structural and specialized proteins).
- Maturation or remodeling phase: starts with the formation of granulation tissue and the reorganization of collagen fibers. This phase can extend for months after the re-epithelialization.

Although these phases are clearly divided for pedagogic needs, on the histologic level they overlap, showing different wound bed phases simultaneously. The correct identification of the stages of healing leads to the accurate choice of coverage.

Tissues Found in the Bed of Wounds

There are two types of tissue that need to be considered in the evaluation of a wound bed.

Viable, which is composed of tissue formed in the healing process aiming at the epithelial reconstruction of the damaged area. These are:

- Granulation tissue: a granulose tissue, bright red, shiny, moist, richly vascularized (Fig. 72.4).
- Epithelialization fabric: new flooring, pink and fragile (Fig. 72.5).

Nonviable, which is the devitalized tissue composed of different organic materials. It can occur in different ways:

- Coagulation necrosis or dry necrosis (eschar): characterized by compressed layer of crusts of hard consistency; usually it can be dried and soft depending on the degree of hydration thereof (Fig. 72.6).

Fig. 72.4 Wound with granulation tissue and exposed tendon

Fig. 72.5 Neuropathic wound with nonviable tissue, granulation tissue, and epithelialization

Fig. 72.6 Leprous wound (reaction) with necrosis

- Necrosis liquefaction or wet or crumbling necrosis: yellowish tissue, whitish, greyish, more slender, soft consistency, and can be

tightly or loosely adhered to the bed and borders, presented as strings, crusting, or mucinous being formed by bacteria, fibrin, elastin, collagen, intact leukocytes, cellular debris, and large amounts of exudate DNA.

There are several instruments used to categorize these types of tissue. We will quote the RYB system, MEASURE, PUSH tool, TIME.

- RYB (Red/Yellow/Black), proposed in 1988 by Cuzzel, which reveals the condition of the tissues: viable and nonviable. Red means that the wound bed is red with a predominance of granulation tissue and new epithelium; the aim of the treatment is to favor the humid environment, protecting the tissue and preventing infection. Yellow: the bed is yellow in color due to the presence of fibrous exudate, devitalized soft tissue, which may be colonized. The goal is to identify the presence or absence of infection; if present institute systemic therapy and promote debridement and cleansing. Black: presence of necrotic tissue with thick eschar formation and requiring removal of this tissue quickly and effectively through debridement [16].
- The acronym MEASURE, where M stands for Measure (measure the length, width, depth, and surface area); E for Exudate (quantity and quality of exudate); A for Appearance (appearance of the wound bed type and amount of tissue); S for Suffering (type and intensity of pain); U for Undermining (presence or absence of detachment); R for Re-evaluation (periodic review of all parameters); E for Edge (conditions of the edges and the adjacent skin) [17].
- The PUSH tool scale (Pressure Ulcer Scale for Healing) is a tool developed in 1996 by NPUAP (National Pressure Ulcer Advisory Panel) that considers the following parameters for the assessment of pressure ulcer: area, amount of exudate, and appearance of the wound bed [18].
- TIME, the T assesses the viability/nonviability of the tissue in the wound bed; I relates to infection, colonization; M to the moisture imbalance; and E the edge of the wound [10].

Therapeutic Approach for Wounds

The care process is quite comprehensive, particularly when it comes to persons with chronic wounds, as they, most of the time, may feel fragile, embarrassed, and ashamed of his/her appearance, all of which goes beyond the physical aspect, affecting the psychological and social demeanor. Therefore, the type of reception the health team grants to these individuals as an attitude has a direct effect on treatment. In fact, a person properly hosted, to whom one pays attention to what they have to say, feels part of the care process. This sort of kindly approach should be used by all professionals working in the institution.

For the successful treatment of wounds, it is necessary for the person to be fully assessed by the multidisciplinary team. The nurse must establish a comprehensive care plan for the treatment and long-term monitoring of these patients [4].

After careful evaluation of the wound it must be cleansed using fluids to remove loosely adherent debris and necrotic tissue on the surface [19–21].

A fluid commonly used for wound cleansing is physiologic solution at 0.9%. Polyhexamethylene biguanide (PHMB) is one of the most advanced technologies for cleaning wounds. PHMB is an antimicrobial belonging to the group of chlorhexidines (biguanide), active against a large number of microorganisms, among them methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and the *Acinetobacter baumannii* that are responsible for multidrug-resistant infections. It is importantly to note that it is biocompatible, i.e., it has no toxicity on living tissues [22].

Other local antiseptics are not recommended. Usually they are chemical products with cytotoxic action that inhibits cell proliferation. Among them one can cite iodine-povidone, acetic acid, chlorhexidine, hydrogen peroxide, and hypochlorite solutions.

Debridement

The debridement consists of removing nonviable tissue, such as necrotic tissue, devitalized tissue,

and colonized bodies and foreign matter, optimizing the healing process and preventing infection.

Types of Debridment (Fig. 72.7)

Enzymatic or chemical debridement is based on the use of proteolytic enzymes (papain, collagenase, fibrinolysin/DNase) which are capable of dissolving devitalized tissues. The choice of enzyme is dependent on the type of existing tissue in the wound.

The application of the selected enzyme should be restricted to the devitalized tissue, avoiding contact with the perilesional areas. For protection of these areas hydrocolloid powder, essential fatty acid oil, or creams that promote a protective barrier can be used. The wound should be covered with a bandage to retain the moisture needed for enzyme action.

Autolytic debridement is obtained by using hydrogels and hydrocolloids that act naturally and selectively. Through the maintenance of moisture, phagocytic cells and proteolytic enzymes are activated, promoting the degradation of nonviable tissue.

Surgical debridement is the method indicated for wounds with large amounts of devitalized tissues. Depending on the severity and extent of the wound, this procedure should be performed by surgeons in the operating room under anesthesia. In superficial wounds, which usually do not require anesthesia, it can be performed on an outpatient basis by medical professionals and trained nurses. Although aggressive, results are faster than with other methods.

Mechanical debridement is also indicated for wounds with large amounts of devitalized tissue. This technique consists in the removal of tissues by application of mechanical strength. This procedure, however, can damage the granulation tissue or already existing epithelialization, and

cause pain. Mechanical debridement methods include negative pressure therapy, wet–dry dressings, hydrotherapy, and irrigation.

Negative pressure therapy involves intermittent and continuous application of subatmospheric pressure at the wound surface. The mechanism of action in promoting the healing is by reducing the superficial edema; improvement of local blood circulation; reduction of excess exudate; stimulating the proliferation of fibroblasts, endothelial cells, and vascular smooth muscle cells; reduction of bacterial load; and favoring wound contraction.

Wet–dry dressings: moistened gauze with saline solution is applied to the wound bed and left until dry. The gauze when removed takes out necrotic tissue. It is a painful method that requires analgesia.

Hydrotherapy uses pulsed and pressurized irrigation. The water is delivered in a continuous or intermittent base under low, intermediate, and high pressure flow.

Irrigation is the steady flow of a solution across a wound bed with the use of a 40 × 12 needle in a 20 mL syringe or a 25 × 8 needle in a 20 mL syringe. The syringe must be positioned in a 45–90° angles and at a distance of 2.5–5.0 cm, which respectively ensure the pressure of 9.5 psi and 13.5 psi, capable of promoting the removal of cell debris, exudates with pathogens, and residues of topically applied creams and ointments which remain in the wound bed. The choice of pressure should vary according to the amount of debris to be removed. In the case of wounds with the largest amount of debris, one should use the 20 mL syringe and a 25 × 8 needle. It is also recommended to use a heated solution to prevent temperature reduction in the wound bed, since a constant temperature of 37 °C stimulates mitosis during granulation and re-epithelialization [23, 24].

Maggot or biological debridement therapy, or maggot therapy, requires the application in the wound bed of larvae reared in the laboratory. The larvae feed on necrotic/devitalized tissue and make selective debridement [10].

Based on the experience of the authors, topical therapy should be decided upon by evaluating the type of tissues, according to the algorithm that follows (Figs. 72.8 and 72.9):
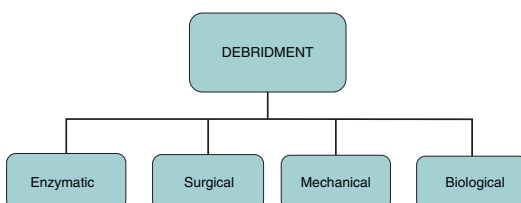
Fig. 72.7 Types of debridment
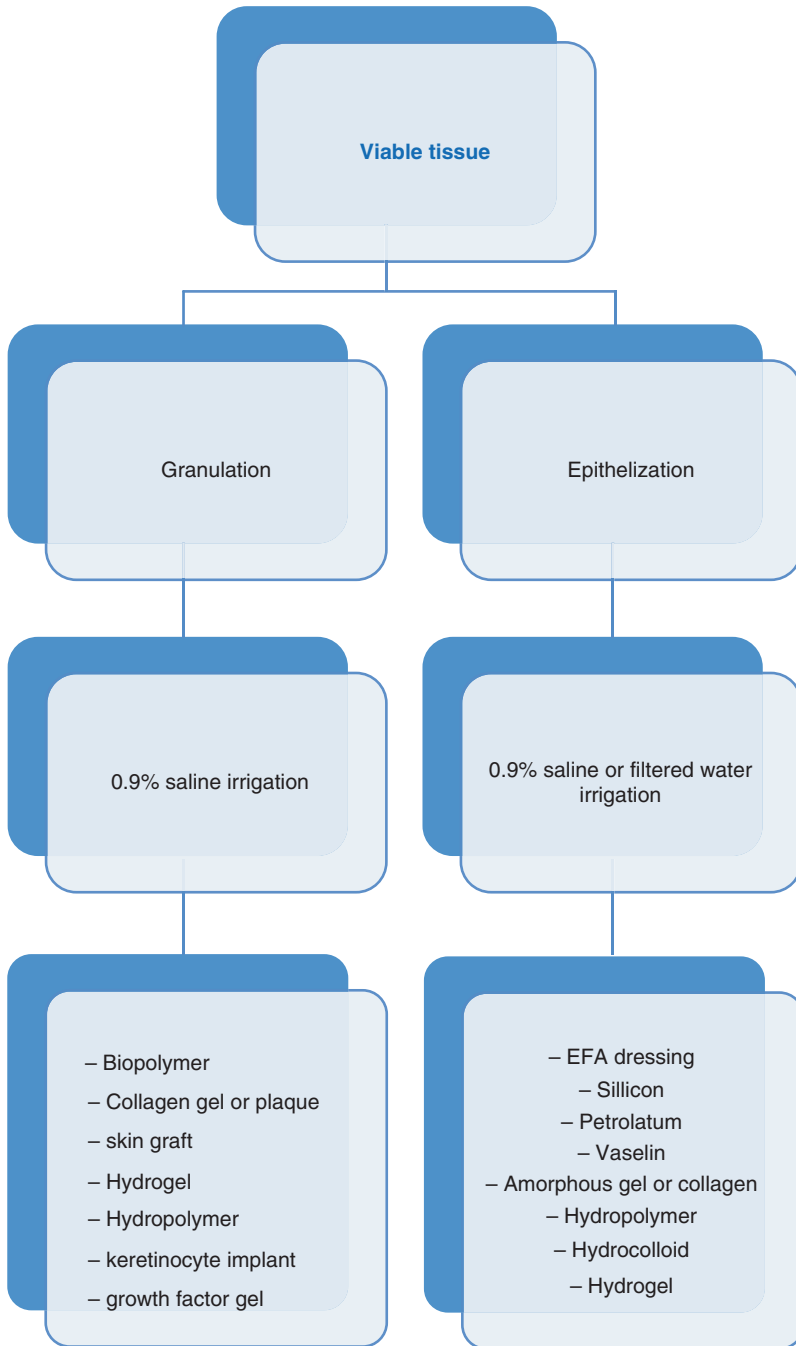
Fig. 72.8 Algorithm for viable tissue
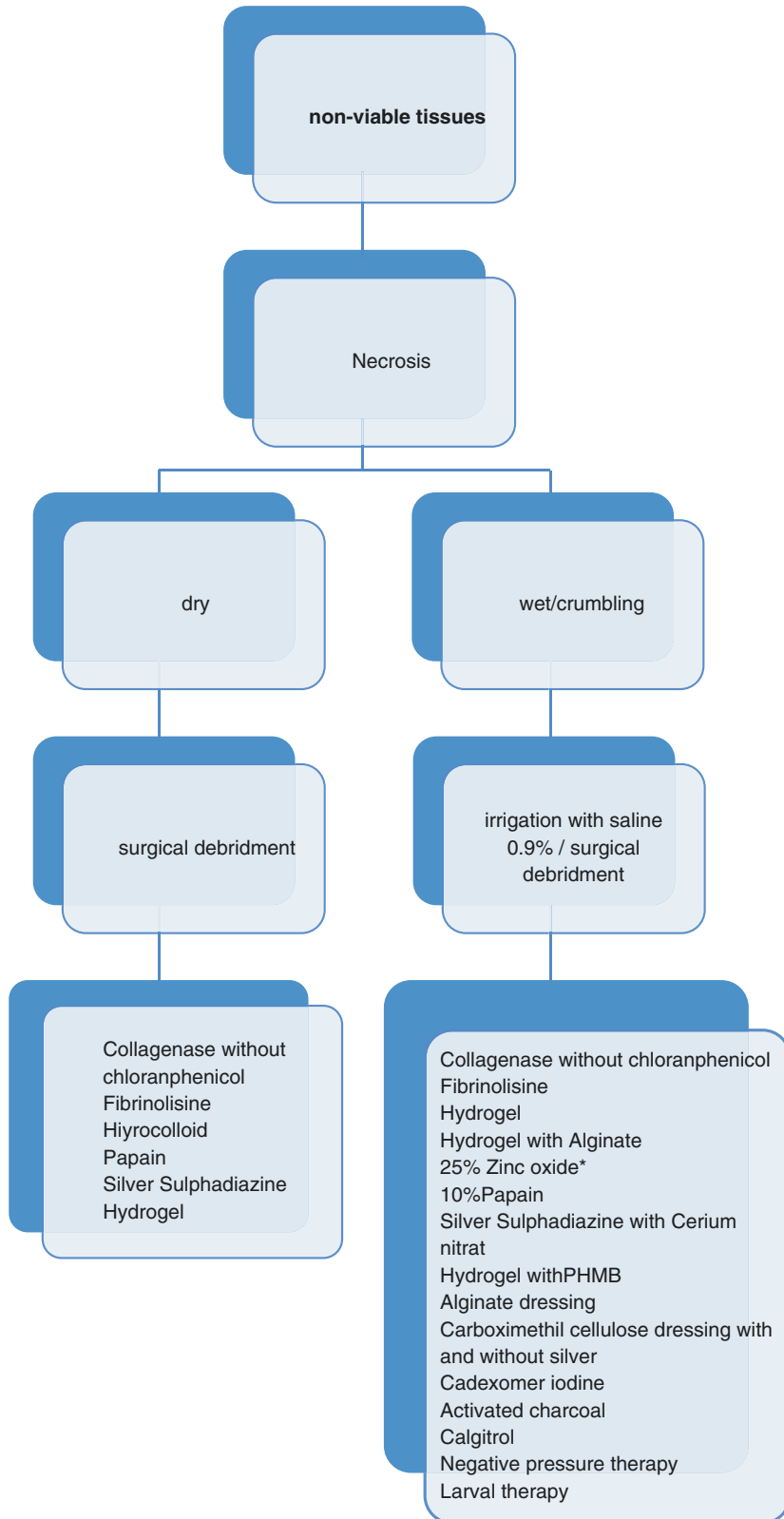
Fig. 72.9 Algorithm for non-viable tissue

Dressings: A Rapid Guide

EFA (Essential Fatty Acids)

Composition: polyunsaturated vegetable oils, linoleic acid, caprylic acid, capric acid, vitamin A and E, soybean lecithin, and lanolin.

Function: transporting materials across cell membranes, which ensures the life of the cell through balanced flow of nutrients and waste products in biological activity.

Indication: protection, hydration, skin restoration, and receiving area graft.

Contraindication: injury to tissue necrosis without debridement, sensitivity to the product.

Change frequency: every 24 h

AGin (Fatty Acids, Unsaturated)

Composition: oleic acid, vitamin A palmitate, DL-α-tocopherol, Vitamin E.

Function: antioxidant activity; protects the cell's DNA particularly in those who are in training; inhibits the free radicals produced by lymphocytes that hinder the process of tissue repair in chronic injuries.

Indication: maintain or restore normal skin characteristics; prevention of skin breaks; moisturizing dry skin.

Contraindication: sensitivity to product.

Change frequency: every 24 h

Hydrogel

Composition: deionized water, glycerin, sodium carboxymethylcellulose, allantoin (natural hydrocolloid).

Function: interacts with the exudate creating moist environment that favors the autolysis, pain relief by moistening the exposed nerve endings in the wound.

Indication: wounds with granulation tissue; with necrotic tissue, venous ulcers, arterial and pressure; second-degree burns of small extent; wounds with partial or total loss of tissue; post-traumatic areas.

Contraindication: patients with sensitivity to product.

Change frequency: 24 h to 3 days depending on the exudate

Hydrogel with Calcium Alginate and Sodium

Composition: calcium alginate and carboxymethylcellulose sodium in an aqueous, transparent, viscous excipient.

Function: keep moist medium, helps in autolysis.

Indication: soften and rehydrate necrotic and devitalized areas of pressure ulcers, stasis, burning of first and second grade, cut, abrasions, and lacerations.

Contraindication: sensitivity to the product, damage to infection and/or secretion.

Change frequency: 24 h for necrotic or very exudative lesions up to 3 days to clean lesions with granulation tissue

Silver Sulfadiazine with Cerium Nitrate

Composition: 0.4% cerium nitrate and silver sulfadiazine 1%.

Function: sulfadiazine (bactericidal and bacteriostatic acting on the bacterial cytoplasmic membrane) effective against Gram-positive and -negative viruses, dermatophyte fungi; cerium nitrate enhances the bactericidal effect.

Indication: devitalized tissue, burn, colonization prevention.

Contraindication: sensitivity to components.

Change frequency: daily in infected lesions and up to 3 days in fresh lesions.

Collagenase

Composition: collagenase, clostridiopeptidase A, and proteolytic enzymes.

Function: acts to selectively degrade the native collagen (necrolysis).

Indication: devitalized tissue: necrosis, fibrosis.

Contraindication: wound healing by first intention, hypersensitivity to enzyme.

Change frequency: every 12 or 24 h.

Fibrinolysin

Composition: bovine emollients, fibrinolysins, deoxyribonucleases, and 1% chloramphenicol.

Function: lytic action of fibrinolysin and deoxyribonuclease dissolve the exudate and necrotic waste.

Indication: devitalized tissue (necrosis, fibrosis).

Contraindication: hypersensitivity to bovine substances.

Change frequency: every 12 or 24 h.

Cadexomer Iodine

Composition: Cadexomer, polyethylene glycol, poloxamer, and iodine.

Function: Cadexomer beads are biodegradable, remove excess exudate and fibrin in the wound base, and reduce bacterial contamination on the surface.

Indication: topical treatment of chronic exuding wounds, infected wounds.

Contraindication: dry necrotic tissue or with known sensitivity to iodine or any of its components; pregnant women, breastfeeding women, children, people with diabetes insipidus, thyroid disorder.

Change frequency: fluid saturation; 72 h.

Zinc Oxide

Function: antiseptic, drying, and anti-inflammatory action, decreased odor and exudate, 25% concentration increases the mitotic index.

Indication: devitalized tissue, abundant exudation, fetid odor.

Contraindication: Hypersensitivity to the product and painful.

Change frequency: every 24–72 h.

Polyhexamethylene Biguanide

Composition: amorphous hydrogel polyhexamethylene biguanide 0.1%, pectin, cellulose.

Function: antimicrobial action (Gram-positive yeasts and fungi), autolytic, wound deodorization, promotes moist environment, facilitates mechanical debridement, stimulates epithelialization.

Indication: chronic wounds or acute, with devitalized tissue, exudative, infected.

Contraindication: none.

Change frequency: daily or up to 3–7 days

Biopolymer

Composition: glyceryl monostearate, cetostearyl alcohol, stearic acid, N-coconut acyl derivatives of L-glutamic acid, sodium acrylate copolymer, hydrogenated polyisobutene, phospholipids, polyglyceryl-10-esters, sunflower oil, hydrogenated olive oil, olive ester, phenoxyethanol, hydrogenated vegetable oil, behenyl alcohol, lecithin, soy sterols, shea butter, fatty acid triglycerides, of *Camelina sativa* oil, dimethicone, hydroxyethylcellulose, disodium EDTA, serum and water *Hevea brasiliensis*.

Function: Gel-cream for skin restoration, has angiogenic activity and accelerating the healing process.

Indication: skin ulcers of various pathologies: arterial, diabetic, mixed, venous, neuropathic, leprous, by pressure, in acute and chronic stages, little exudate.

Change frequency: daily or up to 3 days

Amorphous Collagen Gel

Composition: collagen hydrolysate in a hydrogel matrix.

Function: protective barrier against external contaminants preventing fungal and bacterial proliferation, accelerates healing, and promotes rapid regeneration of the skin after therapeutic and aesthetic dermatologic procedures.

Indication: beaten skin for dermatologic procedures (laser, peeling, or minor dermatologic surgery) or external factors.

Contraindication: sensitivity of formula.

Change frequency: up to 3 days.

Barrier Cream

Function: Protects, moisturizes, and restores the skin's pH, and against maceration.

Indication: perilesional skin for protection against excess moisture that can cause maceration and delayed wound-healing process.

Contraindication: not shown.

Change frequency: daily.

Hydrocolloid Powder

Composition: synthetic resin powder, microgranules, consisting of nonadherent hydrocolloids.

Function: Protects skin with exudate, absorbs moisture caused by chafing.

Indication: to be used in the peristomal skin. It is also indicated in bruised skin.

Contraindication: none.

Change frequency: daily.

Nonadherent Mash Dressing

Function: maintains moist environment, which prevents dehydration of the granulation tissue.

Indication: First- and second-degree burns, grafts, venous ulcers, pressure, eczema, surgical incisions.

Contraindication: sensitivity to components.

Change frequency: several days, depending on amount of exudate.

Sodium Alginate and Calcium

Function: calcium ions and sodium in the blood and exudates interact with the same ions found in the healing, inducing hemostasis, assists in autolytic debridement, promotes absorption of

exudate and maintains the humidity (gel formation).

Indication: pressure ulcers, venous, arterial, diabetic, donor area, and other skin lesions with no hemorrhagic bleeding.

Contraindication: dried injuries and sensitivity to product.

Change frequency: daily changes in infected lesions and lesions cleaned according to saturation.

Coverage Collagen and Alginate

Function: hemostatic properties, stimulates granulation tissue formation, epithelialization, makes healing occur faster.

Indication: treatment of wounds with low to high levels of exudate (pressure ulcers, venous, arterial, diabetic, donor area, and other skin lesions with no hemorrhagic bleeding).

Contraindication: dried injuries and sensitivity to product, and carcinomas.

Change frequency: daily change on exudative lesions and lesions cleaned according to saturation.

Hydrofiber

Function: retains the fluid forming a gel around the fibers, keeps the wound bed moist and warm.

Indication: chronic lesions (pressure ulcers, lower limb), acute injuries (lacerations, incisions, donor area, first- and second-degree burns, and control of small bleeding), highly exudative lesions requiring autolytic debridement.

Contraindication: sensitivity to the product.

Change frequency: up to 7 days.

Hydrofiber with Silver

Function: retain the fluid forming a gel around the fibers, keeps the bed of the wound moist, warm, free of bacteria and odors.

Indication: small abrasions, cuts, lacerations, superficial burns, infections.

Contraindication: sensitivity to the product.

Change frequency: up to 7 days

Activated Carbon and Silver

Function: carbon attracts bacteria and silver combats microorganisms and reduces bacterial colonization and infection control and odor.

Indication: chronic wounds, traumatic and surgical lesions, with or without infection, odor and fibrin.

Contraindication: necrosis, bone exposure.

Change frequency: 7 days.

Natural Biological Film

Function: retains moist environment, does not allow entry of microorganisms.

Indication: burns, wounds, skin graft donor sites.

Contraindication: infected wounds.

Change frequency: single use.

Hydrocolloids

Function: promoting moisture forming a gel that provides for autolysis debridement. It stimulates neogenesis, pH maintenance.

Indication: without infection lesions without exudate, necrosis, prevention of decubitus ulcer.

Contraindication: lesions with infection and/or exudate.

Change frequency: 7 days in clean lesions with granulation tissue.

Hydropolymers

Function: maintain moisture, absorb and retain excess exudate, adhered to the wound bed, preventing maceration, stimulates autolytic debridement.

Indication: no infected lesions, slightly exudative, in granulation tissue and for preventing decubitus ulcer.

Contraindication: lesions with infection and/or secretion.

Change frequency: up to 7 days and, in case of prevention, up to 10 days.

Hydropolymer with Silver

Function: antibacterial, releasing silver ions continuously; exudate is absorbed protecting perilesional area. It has selective permeability (water controls the output and input bacteria), minimizing the risk of infection.

Indication: wounds with moderate to high exudate with delayed healing, with risk or clinical signs of infection, such as leg ulcers, pressure ulcers, second-degree burns, diabetic ulcers.

Contraindication: individuals with allergic reactions to any component of the product.

Change frequency: up to 7 days.

Polyurethane Foam

Function: exchange of ions occurs between the ingredients and silver alginate matrix and wound exudate, leading to the presence of Ag^+ and Ca^{++} ions in the wound bed.

Indication: moist and thermal healing of wounds, infected or colonized; pressure ulcers, venous ulcers, and burns.

Contraindication: hypersensitivity known to alginate or silver, the presence of metals, ulcers due to infectious processes (tuberculosis, syphilis, deep mycoses or third degree burns).

Change frequency: up to 7 days.

Papain

Function: chemical debridement, bacteriostatic, bactericidal, and anti-inflammatory, provides alignment of collagen fibers.

Indication: chemical debridement and facilitator of the healing process, supporting systemic antibiotic treatment of infected wounds. Use concentration of 2% in wound granulation tis-

sue; 4–6% when there is purulent exudate; and 10% when there is presence of necrotic tissue.

Contraindication: sensitivity to the substance or other component of the formulation.

Change frequency: every 12 h.

Growth Factor Gel

Function: acts on the cell membrane (activates the tyrosine kinase that comes into contact with DNA, stimulating cell division and proliferation).

Note: poorly healing ulcers with just partial damage, but with adequate blood supply.

Change frequency: daily, always at the same time.

Unna Boot

Function: reduces edema through the venous pump movement, facilitating venous return, aiding healing.

Indication: venous ulcers of the lower limbs.

Contraindication: arterial and mixed ulcers

Change frequency: every 7 days since there is no discharge or dirt.

Elastic Bandage

Function: reduces edema by means of pump action, making easier venous return and promoting healing.

Indication: treatment of venous leg ulcers and associated conditions where compression therapy indicated.

Contraindication: arterial ulcers and mixed ulcers, leg with circumference of 18 cm below the ankle.

Multilayer Compression Therapy

Function: promotes a recommended therapeutic pressure of 40 mmHg, facilitating venous return and reducing edema.

Indication: venous ulcer.

Contraindication: arterial and mixed ulcer.

Change frequency: up to 7 days.

Glossary

Iatrogenic Inappropriate result from medical procedures or treatments.

Biofilm Community of microorganisms surrounded by a mucopolysaccharidic extracellular matrix, creating a cohesive film in the wound bed that serves as a common defense strategy of these settler microorganisms.

Lipodermatosclerosis Concomitant presence of hard edema and slight pitting (sclerosis).

Maggot therapy Application in the wound bed of larvae of the species *Lucilia sericata* or *Phaenicia sericata* in order to selectively remove the necrotic/devitalized tissue.

Ocher dermatitis Extravasation of red blood cells in the dermis along the deposit of hemosiderin in macrophages.

Enzymes that promote protein breakdown.

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Physical Therapy in Leprosy

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Key Points Summary
- For leprosy patients physical disabilities may lead to a reduction in work potential, restricted social life, and psychological disorders, and are responsible for discrimination against patients
- Early diagnosis, proper treatment, and prevention of disabilities impede the transmission of disease, and reduce disabilities including psychosocial impairment
- Physical rehabilitation and surgery are important tools to prevent disabilities, to improve functional capacity, aesthetics, and social life, and to alleviate pain

Introduction

Nerve damage in leprosy is responsible for a variety of physical injuries and can negatively affect the quality of life of patients [1, 2]. The presence of physical disabilities and the fear of contagion are the main factors responsible for the discrimination that still exists with respect to the disease [3].

Although multidrug therapy (MDT) is effective in the control of leprosy, the elimination of viable bacilli does not mean that patients will not suffer disabilities, including physical disabilities, as functional changes can be caused by reactions even after completing drug therapy. Several factors contribute to the appearance of disabilities, including delayed diagnosis, lack of patient adherence to treatment, and intermittent reactions [4, 5].

In Brazil, 6.5% of all patients diagnosed in 2014 had physical disabilities (grade 2) at the beginning of treatment, which indicates the importance of timely diagnosis of the disease [6]. This demonstrates that health care administrators and professionals need to reduce operational difficulties and investigate new cases in the population so as to minimize the problems caused by late diagnosis.

According to the Brazilian Ministry of Health, in order to prevent disabilities it is essential that the diagnosis is early, that patients receive MDT, and that the medical management and rehabilitation for leprosy reactions are carried out effectively. Moreover, guidance on self-care and

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psychosocial support must be provided. After completing MDT, care must be continued because reactions can occur before, during, and after MDT, often causing irreversible nerve damage and loss of function. These measures should be carried out throughout the healthcare network, from the simplest to the most complex levels, to ensure a good quality of care is provided by a multidisciplinary team acting in an interdisciplinary manner [7].

State of the Art

Pathophysiology of Nerve Damage in Leprosy

Mycobacterium leprae has an affinity for cells that envelop peripheral nerves, the Schwann cells, whose temperature is lower than that of the rest of the body. The most affected nerves in the face are the auricular, trigeminal, and facial nerves; in the upper limbs the ulnar, median, and radial nerves and the superficial branch of the radial nerve; and in the lower limbs the common peroneal and the tibial nerves.

Physical disabilities due to leprosy can be caused by neurogenic and non-neurogenic mechanisms. Neurogenic mechanisms are due to the direct action of the bacillus on the nerve, causing changes in the function of autonomic (hypohidrosis of the skin), sensory (loss of thermal and tactile sensitivity, and pain), and motor (paresis and muscle palsy) nerve fibers. These are considered primary lesions [8]. Secondary lesions are related to the aggravation of these injuries and can include retraction of the soft tissues, trophic and traumatic injuries, infections, burns, and cracks in the skin, among others. Non-neurogenic mechanisms include chronic and acute inflammation arising from leprosy reactions; this may affect the bones, joints, tendons, muscles, ligaments, and internal organs [9].

Face

In leprosy, eye injuries are observed in all clinical forms except the indeterminate form. The facial,

Fig. 73.1 Lagophthalmos

trigeminal, and auricular nerves are most commonly affected. Owing to the direct action of the bacillus, lepromatous leprosy is responsible for more disabilities of the face than the other types of the disease.

Facial Nerve

Motor fibers are responsible for innervations of the facial muscles. Injury to nerves may be complete, unilateral, or bilateral. Generally in leprosy, only the orbicularis oculi, the muscle that closes the eyelids, is affected; initially only paresis is felt by the patient but the condition evolves to paralysis of the muscle. In this case, the patient may experience an eyelid cleft due to lagophthalmos, the inability to close the eyelids completely (Fig. 73.1), which can be mild (up to 2 mm) or severe (≥2 mm). Other possible ocular manifestations are redness, itching, burning, a gritty feeling, and decreased visual acuity [10]. The autonomic fibers are responsible for the stimulation of the lacrimal, nasal, and salivary glands.

Trigeminal Nerve

The trigeminal nerve divides into three branches, the ophthalmic, maxillary, and mandibular branches, and is responsible for sensitivity of the cornea, nose, mouth, teeth, and tongue [11]. One feature of its injury in leprosy is diminished or complete loss of corneal sensitivity with complaints such as decreased or absent automatic blinking of the eyelids, decreased visual acuity, hyperemia, and corneal ulcers.

Nose

Involvement of the facial nerve is responsible for autonomic and motor abnormalities and damage to the trigeminal nerve causes the loss or reduction of nasal sensitivity. Primary changes to the nose may occur due to the replication of bacilli in the nasal mucosa resulting in obstructive infiltration, viscous secretion, crusts, and ulcerations. In more advanced stages, secondary injuries can occur such as destruction of the nasal cartilage, nasal septum perforation and collapse of the nasal pyramid. This disability can be one of the factors responsible for social exclusion of patients [12].

The Arms

The most affected nerve trunks of the upper limbs are the ulnar nerve followed by the median nerve and more rarely the radial nerve. Impairment of muscle strength and sensory afferent caused by damage to these nerves change grip patterns causing difficulties in using the hands, with limitations to perform activities of daily life and work and consequently restrictions in social participation [13].

Ulnar Nerve Injury

In the arm, the most commonly affected nerve in leprosy is the ulnar nerve with its point of greatest vulnerability being the elbow, where it is close to the surface, relatively fixed, and passes by a joint. The predisposing anatomy in this region associated with the biomechanics of the ulnar nerve, which is subjected to traction and friction during movements of the elbow, the most important factors that cause neural compression.

The clinical manifestations of this injury are changes to sensory, motor, and autonomic functions in the hypothenar region, the fourth (medial) and fifth fingers and the area of the back of the hand corresponding to these fingers. The dorsal cutaneous branch is found in the lower third of the forearm [14, 15].

The intrinsic muscles of the hand are innervated largely by the ulnar nerve and, as a morphologic characteristic, its paralysis causes flexion of the fingers and hyperextension of the metacarpophalangeal joints represented by palsy of the dorsal and volar interosseous muscles, medial lumbrical muscles (fourth and fifth digits), adductor pollicis and the deep portion of the short flexor of the thumb, and the opponens pollicis of the fifth digit, leaving the common extensor digitorum to function in an unbalanced manner; this results in the hand having a claw-like look [15].

This imbalance results in bending of the fourth and fifth digits with hyperextension of the metacarpophalangeal joints and flexion of the interphalangeal joints because of the isolated action of the flexor and extensor muscles due to intrinsic paralysis (Fig. 73.2). With the unbalanced forces, the medial edge of the hand loses the transverse and longitudinal radius, making it impossible to hold cylindrical objects in the hand. Precise pinch

Fig. 73.2 Claw fingers (fourth and fifth) and atrophy of the first intermetacarpal space. Fig. 73.2 Froment's sign

grip is impaired with an inability to stabilize thin objects between the thumb and forefinger resulting from paralysis of the adductor and half of the short flexor muscle. Owing to the force applied when holding an object between the thumb and forefinger, there will be marked flexion of the distal phalanx of the thumb reflecting the instability of the metacarpophalangeal joint; this is known as Froment's sign (Fig. 73.2a) [13].

With the grip strength to hold cylindrical objects impaired and the lack of precision to grip small objects as a result of ulnar nerve injury, the strength of the hand is reduced by 40–70% [13].

As a result of the functional imbalance, the patient develops different ways to hold objects to become independent. However, often the individual uses areas of contact that were not designed to hold things, such as the back of the hand and the fingertips. The quest for independence using nonfunctional movements can affect the physical integrity of the individual in the future [13, 16].

Another important morphologic characteristic is the atrophy of the first dorsal interosseous muscle, which may cause social exclusion of the patient (Fig. 73.2).

Median Nerve Injury

Nerve compression occurs in the transverse and annular carpal ligaments [17]. This injury causes sensory, motor, and autonomic changes in the volar region, the thenar eminence, the thumb and the region of the palm corresponding to the second and third digits and the side of the fourth digit, as well as of the back of the hand in the region of the middle and distal phalanges of the second and third digits. The paralysis of this nerve in leprosy commonly occurs after ulnar nerve injury [18].

The characteristic of median nerve damage is the loss of opposition and abduction of the thumb caused by palsy of the short abductor, opponens, and short flexor (superficial portion) muscles which normally maintain the thumb on the same plane as the hand, making it impossible to grasp objects (Fig. 73.3). This paralysis results in serious disability, as the thumb is responsible for 50% of the hand functionality [18, 19].

Fig. 73.3 Loss of opposition of the thumb

All the intrinsic musculature of the hand is affected by paralysis of the median ulnar, resulting in an imbalance of the extrinsic muscles causing functional disorders. In these cases, the function of the hand is reduced to that of a hook; objects are held with the fingers in adduction or between the fingers (interdigital) with practices unique to each patient.

Injury to the Radial Nerve

Compression of the radial nerve occurs in the humeral medullary canal, located in the middle third of the arm. Its sensory distribution corresponds to the central area of the back of the arm as far as the olecranon and posterior and central regions of the forearm. It is responsible for the innervations of the muscles of the arm and forearm used for extension and supination movements.

The morphology of radial nerve injury is drop wrist caused by paralysis of the extensor muscles of the wrist and fingers, which makes it difficult to hold objects [20].

This reaction occurs in only 1% of leprosy cases and generally occurs after injury to the ulnar and median nerves, a condition known as triple paralysis [18].

Injury of the superficial radial nerve branch causes loss of sensation in the posterior region of the thumb and the radial edge of the back of the hand.

Lower Limbs

The most affected nerve trunks of the lower limbs related to leprosy are the common peroneal nerve that branches out into the deep and superficial peroneal nerves, and the tibial nerve which subdivides in the plantar region of the foot as the medial plantar, lateral plantar, and calcaneal nerves. These two nerve trunks with their respective branches stimulate all the extrinsic and intrinsic muscles of the foot. Duerksen, after experience in Brazil and Paraguay, states that the most commonly affected nerve in the lower limb in leprosy is the tibial trunk [21].

Different levels of nerve damage result in changes in physiologic gait patterns from a slight reduction in sensitivity (the patient does not notice the loss of a slipper, for example) to paralysis resulting in foot drop gait, which is very susceptible to falls and traumatic injuries. The limitation in the ability to walk makes patients, apart from having a risk of further injury, restricted in their participation of social activities [13].

Common Peroneal Nerve

The common peroneal nerve is a branch of the sciatic nerve that runs down the side of the popliteal fossa and then winds around the fibula neck and passes through an osteofibrous opening known as the fibular tunnel, where it penetrates the superficial belly of the peroneal muscle. Inside this tunnel, the nerve divides into two branches, the deep and superficial branches. This section of the nerve is closer to the surface and susceptible to the installation of *M. leprae* causing nerve damage.

The common peroneal nerve muscle group is represented by the tibialis anterior muscle, the extensor digitorum longus and brevis, and the extensor hallucis longus, and the innervation of the superficial peroneal nerve is represented by eversion of the foot muscles. Regarding the sensory distribution, the area corresponding to the trajectory is the anterolateral region of the leg, foot, and toes, including the medial side of the hallux.

The clinical features of injury to the common peroneal nerve are sensory and autonomic loss in
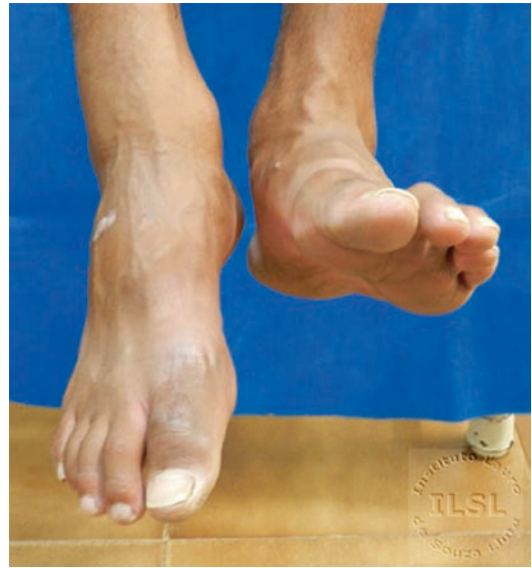
Fig. 73.4 Foot drop

the area of its distribution. An inability to perform dorsiflexion of the foot and extension of the toes, classically known as "foot drop," is observed in complete nerve lesions (Fig. 73.4).

The physiologic gait is represented by phases with each one having a key role in walking: the stance phase, when the heel touches the ground, the swing phase, the exchange stage, and the propulsive stage, when the forefoot produces leverage for the next step. With nerve palsy, the gait pattern becomes pathologic and the phases are changed with the forefoot being the first to touch the ground.

With changes in the gait, the patient is at risk of injury from loss of balance and falls, with twisting and shortening of the flexor unit leading to fixed deformities.

Tibial Nerve

The tibial nerve leaves the popliteal fossa similar to the common peroneal nerve, but its trajectory is deep in the gastrocnemius and soleus muscles. However, as it passes through the tarsal canal, it is close to the surface with an aggravating anatomic constriction.

The clinical characteristics of injuries to the tibial nerve are sensory and autonomic changes

Fig. 73.5 Claw toes

in the plantar region of the foot. This trunk after going around the medial malleolus is divided into three branches: medial plantar, lateral plantar, and calcaneal nerves.

Motor alterations are apparent in the intrinsic muscles of the foot (interosseous and lumbrical). When paralyzed, the patient evolves with flexion of the interphalangeal joints and extension of the metatarsophalangeal joints (Fig. 73.5). Intrinsic paralysis associated with loss of sensitivity can cause the patient to develop severe trophic and traumatic injuries with devastating consequences, which may even lead to amputation after osteomyelitis.

Assessments and Preventive Measures

Instruments and measures to evaluate and monitor leprosy patients as recommended by the Brazilian Ministry of Health consist in the Simplified Neurologic Assessment (SNA), evaluation of the Degree of Disability (World Health Organization (WHO)), the Screening of Activity Limitation and Safety Awareness (SALSA)

scale, and the Participation Scale, as well as the application of basic prevention, control, and treatment strategies.

In leprosy, most of the problems resulting from injury to peripheral nerves can be avoided using the SNA to evaluate the situation of the nerve and neural function [22].

By means of this assessment, changes in neural function can be monitored, that is, routinely analyzed to identify neural inflammation early so as to prescribe the necessary treatment, monitor response to the treatment of neuritis, and determine the need for surgical intervention [22, 23].

The degree of disability, as proposed by Bechelli and Dominguez and standardized by the WHO, is a measure that indicates decreases or loss of sensation and muscle strength, and visible deformities; it is widely used in planning actions to prevent disabilities and as an epidemiologic indicator. The degree of disability related to injuries to the eyes, palms of the hands, and soles of the feet is assessed by this instrument because these are considered the areas that are most susceptible to injuries during daily activities [22].

According to Deepak, in addition to physical disabilities, 20% of patients with leprosy may also have psychosocial restrictions [24].

One screening instrument, the SALSA scale, was developed to assess how disabilities interfere with the activities of daily life of patients. This scale allows a measurement of the extent to which activities are limiting and the risk of worsening disabilities while carrying out activities. This scale is based on the International Classification of Functioning, Disability and Health (ICF) [10]. It was developed, tested, and validated in six languages, Chinese (Mandarin), English, Hausa, Hebrew, Tamil, and Portuguese (Brazil). The scale consists of 20 questions with the score ranging from 10 to 80. A low score indicates little difficulty, while higher scores indicate increasing limitations to perform activities.

The data collected using these instruments are part of the process of diagnosing, monitoring, treating, and preventing peripheral nerve injuries.

The Participation Scale (version 4.6), developed after anthropologic field work, aims to quantify restrictions in social participation experienced

by people affected by leprosy and to assess the severity of the social needs of patients with disabilities.

The scale was subjected to psychometric tests of validity, reliability, and stability and was validated for use in India, Brazil, and Nepal after a multicenter study. It includes several domains of the ICF such as learning and applying knowledge, communication and self-care, mobility, domestic life, interpersonal interactions and relationships, major life areas, and community [25].

This scale consists of 18 items with scores ranging from 0 to 90 points, and takes about 20 min to apply. A score of from 0 to 12 points is considered unrestricted social participation, from 13 to 22 mild restriction, from 23 to 32 moderate restriction, from 33 to 52 severe, and scores from 53 to 90 completely restricted [25].

As rejection can begin in the family, in society, or even in the patients themselves, it is necessary to know the social participation of these patients and to determine the degree and nature of possible restrictions.

Simplified Neurologic Assessment

The SNA must be systematically carried out on a regular basis as part of leprosy control measures. This assessment is important because nerve damage can be very subtle and go unnoticed by the patient at the time of diagnosis, during treatment, and even after the end of treatment.

Neurologic assessments should be performed at diagnosis, that is, at the beginning of treatment, every 3 months during treatment if the patient does not complain, at discharge, and after completing MDT for up to 5 years. When neuritis or reactions are seen or suspected or when the patient complains, this assessment should be performed every month or more often if possible [22]. Additionally assessments should be performed at 15, 45, 90, and 180 days after neural decompression [26].

The minimum content of the SNA for the eyes, hands, and feet is based on the verification of the main complaint, inspection, evaluation of sensitivity, motor evaluation, nerve palpation, and evaluation of the degree of disability.

Patient complaints and the inspection conducted by the examiner are important, as they are correlated to the clinical picture and help to identify nerve damage early.

Investigation of the Main Complaint

Patients should be questioned about their complaints in relation to the nose, eyes, hands, and feet. The most frequent complaints in the nose are respiratory obstruction, dryness, crusts adhered to the nasal mucosa, and bleeding. In the eyes there are reports of a gritty feeling, burning, itching, watery eyes, decreased vision, redness, and pain. Complaints related to the hands and feet include pain, paresthesia, hypoesthesia, and paresis, or patients may report that they drop objects frequently or slippers fall off without them noticing.

Inspection

During the inspection of the outside of the nose, check the skin conditions and for the presence of lepromas, infiltration, hyperemia, ulceration, scarring, and collapse of the nasal pyramid.

During the examination of the eyes, look for hyperemia of the conjunctiva, lagophthalmos, ciliary and supraciliary madarosis, dryness and corneal ulcers, trichiasis, ectropion, entropion, and corneal opacity.

Edema, scars, skin cracks, sores, loss of hair, dry skin, cyanosis, atrophy, resorption, retractions, and morphologic characteristics of neural injury are investigated on the hands and feet.

Nerve Palpation

There is no laboratory gold standard for the diagnosis of leprosy, but a smear, which identifies the presence of *M. leprae* in lymph, and histopathology of tissue, support clinical findings which are still essential to arrive at a diagnosis. In the physical examination skin lesions, a decrease or complete loss of protective sensation, muscle strength, and thickening of peripheral nerves must be carefully investigated.

Early diagnosis of nerve thickening by palpation of the nerve trunks near the surface of the skin

Table 73.1 Palpation techniques

Nerve	Position	Local
Ulnar	Upper limb at 90–120° of flexion. The examiner supporting the patient's forearm in his hand	Proximal and distal trajectories of the nerve, in relation to the ulnar groove. (epicondylar groove) (Fig. 73.6)
Median	Position the patient's wrist at about 10° of flexion	Wrist between long palmar tendons and flexor carpi radialis (Fig. 73.7)
Radial	Position the shoulder with internal rotation and keep the elbow flexed with the forearm in pronation and supported by the examiner	Spiral canal in the rear middle third of the arm (Fig. 73.8)
Peroneal	Sitting with the knees flexed at 90° and feet flat on the floor	Back of the leg between the head and neck of the fibula (Fig. 73.9)
Tibial	Sitting with knees at 90° of flexion and inversion and passive plantar flexion	Medial malleolus, behind and below the bony prominence (Fig. 73.10)

Source: (Brazil, 2008; Baccarelli R, Marciano LHSC, 2003)

Fig. 73.6 Palpation of the ulnar nerve

Fig. 73.7 Palpation of the median nerve

Fig. 73.8 Palpation of the radial nerve

allows the immediate institution of drug therapy and rehabilitative interventions (Table 73.1).

At the time of palpation the examiner should observe the patient's facial expression in relation to their pain threshold. Bilateral palpation is rec-ommended in order to compare the left and right sides to identify nerve thickening, consistency, nodules, and Tinel's sign, a local tingling electric shock sensation [27].

Fig. 73.9 Palpation of the common peroneal nerve

Fig. 73.10 Palpation of the tibial nerve

It is worth noting that the median nerve is rarely palpable, as it has a deep trajectory between the superficial and deep flexor tendons. The assessment of this nerve is conducted to verify the presence of pain on palpation, or a positive Tinel's sign. The radial nerve also passes along a deeper bed, and its

palpation demands skill and experience of the examiner.

Sensitivity Assessment

In leprosy, the sensory evaluation can be limited to points representative of the sensory distribution of the ulnar, median, radial, peroneal, sural, and tibial nerves to diagnose and monitor nerve injury (Fig. 73.11).

Evaluation of Corneal Sensitivity

The sensitivity of the cornea should be tested to assess possible trigeminal nerve damage in leprosy. Therefore, we recommend the use of thin tasteless dental floss. The dental floss should measure 5 cm plus a length sufficient for the examiner to hold. The patient is asked to look at the forehead or the finger of the examiner. Then pull the dental floss in the temporal periphery of the cornea and observe whether blinking is immediate, delayed, or absent (Fig. 73.12).

Sensitivity Test for the Hands and Feet

The sensitivity test of the hands and feet is performed using Semmes-Weinstein (S-W) monofilaments. This is considered one of the most reliable tests and is valid for field work. It is a standardized and quantitative test adopted for the diagnosis of nerve disease by the International Society for Peripheral Neuropathy.

According to Moberg, the test is reliable in 84% of cases. Compared with other electrophysiologic studies, this test is a safe and inexpensive method of evaluation with high sensitivity, specificity, and reproducibility [28]. The S-W test is a subjective test, i.e., it depends on the concentration and cooperation of the individual being assessed, a condition that should be highlighted, given that it can be a factor in the accuracy and reliability of the test.

S-W monofilaments consist of 38-mm lengths of nylon yarn (No. 612) with different diameters. Commercially they are bought as kits of 5, 6, or 20 monofilaments.

Werner and Omer [29] found that clinically you can use a small number of monofilaments to evaluate peripheral sensitivity without affecting

Nerves: 1,2,3- ulnar; 4,5,6- median; 7- radial   Nerves: 1-9 - tibial; 10- peroneal; 11- sural
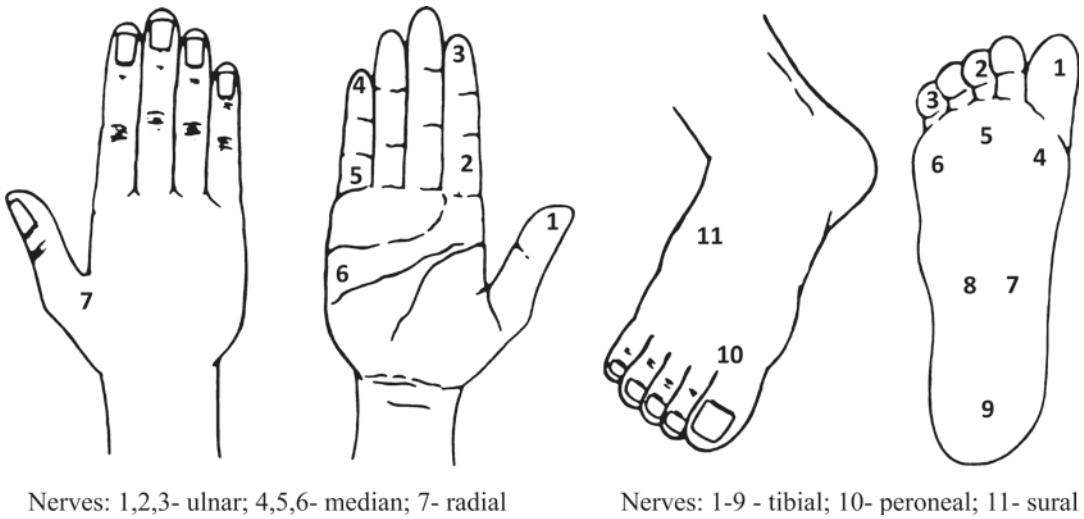
Fig. 73.11 Points representative of the sensory distribution of the ulnar, median, radial, tibial, peroneal, sural nerves

Fig. 73.12 Corneal sensitivity study

the outcome. In Brazil, the National Coordination of Sanitary Dermatology includes a set of six monofilaments as a source to assess sensitivity in leprosy.

On being applied perpendicularly to the skin, when the monofilament bends slightly, forces of 0.05 g, 0.2 g, 2.0 g, 4.0 g, 10.0 g and 300 g are exerted in the area being examined depending on the thickness of the thread (Fig. 73.13) [30].

Von Prince and Butler [31] conducted comparative studies of the S-W monofilaments and other tests such as temperature, static two-point discrimination, proprioception, stereognosis, pain and graphesthesia in patients with peripheral neuropathy. This comparison allowed the calculation of functional levels, as shown in Table 73.2.

Motor Assessment

Voluntary muscle testing is reliable to evaluate neural function. It is valid to identify conduction blocks or larger axonal losses. Motor deficiency is identified after 30% of the fibers are affected [32, 33].

Daniels and Worthingham [34] recommend a muscle strength grading scale of 0–5 (Table 73.3).

The hand and foot muscles that must be evaluated for the SNA are described in Table 73.4. This assessment includes a muscle for each nerve that is generally affected by leprosy, but can be expanded depending on the needs of each individual.

Classification of the Degree of Disability (WHO)

The degree of disability is a measure that indicates the loss of protective sensation and visible deformities resulting from neural injury including blindness. It is an epidemiologic indicator used to evaluate leprosy control programs, determine early diagnosis of the disease, and compare the degree of disability at the start of treatment and at discharge to determine whether there has been an improvement or not [26].

Using the first physical evaluation and the sensory and motor assessment of the eyes, hands, and feet, it is possible to classify the degree of disability of the patient following the criteria of the WHO, as described in Table 73.5.

Fig. 73.13 Semmes–Weinstein monofilaments

Table 73.2 Semmes–Weinstein monofilament, registration code, and functional level

Monofilament (grams)	Registration code	Functional level
0.05 g	🟢	Normal sensitivity of the hand and foot
		Conserved two-point discrimination, fine texture discrimination, stereognosis, thermoesthesia, feeling deep pressure and kinesthesia
0.2 g	🔵	Decreased sensitivity in the hand and normal in the foot
		Loss of graphesthesia
		Difficulty with two-point discrimination and fine texture discrimination
2 g	🟣	Decreased protective sensitivity in the hand
		Loss of two-point discrimination and fine texture discrimination
		Affected stereognosis and thermoesthesia
0.4 g	🔴	Loss of protective sensation in the hand and sometimes in the foot
		Loss of stereognosis and thermoesthesia
10 g	⊗	Loss of protective sensation in the foot
		Loss of thermoesthesia
300 g	○	Presence of the feeling of deep pressure on hand and foot
		Painful sensitivity may be present
		Preserved kinesthesia
Does not feel the touch of 300 g monofilament	●	Loss of sense of deep pressure on hand and foot
		Painful sensitivity and kinesthetic may be present

Simple Techniques to Prevent Disability and for Self-Care

The basic conducts and the procedures to treat changes in autonomic, sensory, and motor functions are shown in Tables 73.6, 73.7, and 73.8.

Exercises

In cases of paresis and paralysis, the prescribed exercises should be passive, assisted active, active, and active resistant, according to the degree of voluntary muscle strength. The exercises related to the muscles described are shown in Table 73.9.

Table 73.3 Degree of voluntary muscle strength and functional status

Degree of muscle strength	Functional description	Functional status
5	Full motion against gravity with maximum resistance	Normal
4	Full motion against gravity with partial resistance	Paresthesia
3	Full motion against gravity	
2	Partial movement	
1	Muscle contraction without movement	
0	Without evidence of muscle contraction	Paralysis

Source: Ordinance No. 3125, GM/Ministry of Health 7/10/2010

Table 73.4 Motor assessment of main muscles innervated by the facial, ulnar, median, radial and peroneal nerves

Nerve	Muscle	Action	Test
Facial	Orbicularis muscle of the eye	Eyelid occlusion	Ask the patient to close the eyes gently, while the examiner assesses whether the eyelids close completely or not with the help of a spotlight that should be placed at an inferior oblique angle
Ulnar	Abductor of the 5th finger	Abduction of the 5th finger	Position: forearm and palm down. Hold the 2nd to 4th fingers and ask the patient to move the 5th finger away as a counter force is applied, from the outside at the second phalanx, returning the finger to the plane of the hand. Ideally, the metacarpophalangeal joints should be at 30° of flexion (Fig. 73.14)
Median	Pollicis brevis	Abduction of the thumb	Position: forearm and palm facing up and resting on a table. The patient raises the thumb from the hand plane forming an angle of 90°, and then apply opposing force to the lateral edge of the base of the proximal phalanx forcing it down (Fig. 73.15)
Radial	Wrist extensors	Wrist extension	Position: forearm and palm down. The patient raises his wrist, leaving the fingers relaxed. After this movement, resistance is placed at the back of the hand in the direction opposite to the movement performed. (Fig. 73.16)
Peroneal	Extensor hallucis	Extension of the hallux	Position: patient sitting with the knee in flexion. The examiner, after stabilizing the foot and ankle in neutral, asks the patient to elevate the hallux as much as possible, applying counter resistance on the dorsum of the proximal phalanx of the toe (Fig. 73.17)
	Tibialis anterior	Dorsiflexion of the foot	Position: patient sitting with the knee in slight flexion. After stabilizing the leg, ask the patient to lift the foot, keeping the toes relaxed. Resistance should be applied on the medial side of the dorsum of the foot (Fig. 73.18)

Source: Brazil, Disability Prevention Manual, 2008

Fig. 73.14 Strength test for the abductor muscle of the fifth finger

Fig. 73.15 Strength test for the abductor pollicis brevis muscle

In both paresis and paralysis, the muscles of the hand and foot may suffer muscle-tendon shortening and periarticular retraction resulting in joint limitations. These problems can be avoided or minimized by stretching exercises.

One of the techniques for stretching the flexor muscle tendon units of the wrist and fingers is that the patient supports the hand on a table and uses the other hand to keep the fingers in extension as far as possible. At the same time the patient must keep the elbow in extension. Thus, a gradual lengthening of these units will be produced (Fig. 73.26).

Stretching the muscle tendon units of the lower limbs should be carried out in the flexor

Fig. 73.16 Muscle strength test for the wrist extensors

Fig. 73.17 Strength test for the extensor hallucis muscle

Fig. 73.18 Strength test for the anterior tibialis muscle

Table 73.5 World Health Organization disability grade

Degree	Characteristics
0	Eyes: muscle strength of the eyelids and corneal sensitivity preserved and patient can count fingers at 6 m or visual acuity ≥0.1 or 6:60
	Hands: muscle strength of the hands and palmar sensitivity preserved; can feel a 2 g monofilament (purple) or the tip of a ball point pen
	Feet: muscle strength of the feet and plantar sensitivity preserved; can feel a 2 g monofilament (purple) or the tip of a ballpoint pen
1	Eyes: decreased muscle strength of the eyelids but without visible disabilities or diminished or loss of corneal sensitivity: delayed or missing response to touch using dental floss or decrease/absence of blinking
	Hands: decreased muscle strength of the hand without visible disabilities or impairment of palmar sensitivity: does not feel a 2 g monofilament (purple) or the tip of a ballpoint pen
	Feet: decreased muscle strength of feet with no visible disabilities or altered plantar sensitivity: does not feel a 2 g monofilament (purple) or the tip of a ballpoint pen
2	Eyes: visible disability caused by leprosy, such as lagophthalmos, ectropion, entropies, and trichiasis. Central corneal opacity; iridocyclitis or cannot count fingers at 6 m or visual acuity <0.1 or 6:60, without other possible causes
	Hands: visible disability caused by leprosy, such as claw fingers, bone resorption, muscle atrophy, wrist drop, contracture and wounds
	Feet: visible disability caused by leprosy, such as claw toes*, bone resorption, muscle atrophy, foot drop, contracture, and wounds

Source: General Coordination of Leprosy and Diseases in Elimination-CGHDE/DEVIT/SVS/Ministry of Health

(Fig. 73.27a). Another option for stretching is shown in Fig. 73.27b.

Other measures may be necessary, such as the use of orthosis, adaptations, and reconstructive surgeries.

Assistive Technology

According to Bersch [35], assistive technology is an aid that will enable a desired function that has been prevented by circumstances such as disability or aging to be performed.

muscles of the ankle and foot. In this case the patient should stand facing a wall with the leg to be stretched behind with the knee in extension. The other leg must be placed in front of the body with the knee in flexion. From this position the patient should move the body forward flexing the elbows without taking the heels off the floor

Table 73.6 Signs and conducts in ocular changes

Signs	Conducts	Procedures	Objective
Dryness of the cornea	Artificial lubrication with eye drops and ointment	Keep the patient sitting and looking up. Retract the lower eyelid from the temporal portion and apply an eye drop, being careful not to touch the eye with the tip of the bottle	Eye lubrication
	Blink frequency	The patient should close the eyes gently for 30 s	
Trichiasis	Removal of lashes	Removal of upper eyelashes: patient sitting, looking down remove each lash facing the eyeball using eyebrow tweezers and a magnifying glass. Then lubricate	Prevent ocular lesions, in particular corneal ulcers
		Removal of lower lashes: Patient sitting, looking up. Follow the procedures above	
Initial lagophthalmos	Exercises to open and close the eyes	Ask the patient to gently close the eyes and then close with as much force as possible. Stay with the eyes closed for 5 s. Repeat 20 times the same exercise three times a day until complete recovery of the strength of the orbicularis oculi muscle	Strengthening of the orbicularis oculi muscle

Table 73.7 Signs and conducts in changes of the nose

Signs	Conducts	Procedures	Objective
Dry nasal mucosa	Hydration and lubrication	Put water in cupped hand or in a container, breathe in water and then let it drain (Fig. 73.19). Use cream or Vaseline at the entrance of the nostrils and gently massage the outer portion with the finger. The patient should be instructed not to blow the nose hard and not insert objects into the nostril to remove scabs, as this can damage the mucosa	Facilitate the removal of secretion, avoiding the accumulation, burning, dryness and crusting
Hypersecretion			
Crusts	Hydration and lubrication. Warn the patient not to remove crusts with the finger or objects such as cotton swabs, etc.		Remove the crust adhered maintaining the nasal cavity clean and free from ulcers
Ulcers	Clean to remove crusts and applying antibiotic ointment (provided by the doctor). Recommendation: repeat until healed		Prevent secondary infection

Fig. 73.19 Nasal hydration

Orthoses and Adaptations

Orthoses are devices externally applied to a limb to immobilize one segment, balance deforming forces, and assist manual function.

In leprosy, orthoses are indicated when paresis or paralysis is severe, and in cases of neuritis, leprosy reactions, injuries, infections, retractions of joints, postoperative neural decompression, and reconstructive surgeries. Some orthoses are shown in Figs. 73.28, 73.29, 73.30, 73.31, 73.32, 73.33, and 73.34.

The use of adaptations is recommended when sensory or motor disorders are present; these are simple modifications to personal working tools as well as insoles or adapted shoes. The objectives of these adaptations are to promote or facilitate functional independence, improve the grip or gait, and prevent or

Table 73.8 Signs and conducts in the skin changes of the hands and feet

Signs	Conducts	Procedures	Objective
Hyperkeratotic dry skin	Hydration lubrication massage	Immerse the limb in water at room temperature for 10 min. Then wipe off the excess of water and apply an oily or creamy substance to prevent the evaporation of water performing a sliding massage (Fig. 73.20)	To improve hydration and lubrication of the skin to avoid cracks and wounds
		This is not recommended when there are skin or nail lesions, or other dermatitis	
	Removal of calluses	After hydration, remove calluses using sandpaper being careful not to cause injuries. Remove only the surface layer of skin. Then lubricate the skin	Reduce points of over pressure
Loss of protective sensation	Training visuomotor	Guide the patient on how to use the vision to compensate for sensory impairment and reduce difficulties in manual skills	Improve functional performance
	Coordination		
	Adaptations	Encourage the patient to use adaptations of tools for work and personal use, simple insoles in comfortable oversized shoes	Prevent secondary injuries

Fig. 73.20 Hydration, lubrication, and sliding massage

stop the worsening of disabilities (Figs. 73.35, 73.36, 73.37, and 73.38).

Self-Care

To prevent disabilities in leprosy it is necessary to change the behavior; this is difficult, especially in adults. Prevention is achieved by the professional winning over the patient's confidence and incorporating strategies to perform activities of daily life. Thus the professional needs to proceed with care, using the correct approach to preventive measures with the aim that they will truly be assimilated by the patient as a new conduct in daily life in order for them to become normal routine activities in day-to-day life. An essential feature is to adapt preventive measures to use available materials and

related to the patient's culture, as in this way success is facilitated [36].

To reduce the damage caused by leprosy, it is essential that patients develop the habit of caring for themselves day by day.

From the conditions of the patient and knowledge of individual problems of each member of the group, group interventions are geared to increase the patient's knowledge about the disease, clarify and advise on treatment methods and self-care practices, promote and/or restore functional performance in occupations that make up the daily lives of individuals, through dynamic actions, lectures, recreational activities, role playing, and strategies to follow at home, as well as to prescribe or create orthoses and adaptations of work and daily life instruments. All of these

Table 73.9 Exercises

Muscles	Resisted: grade 4	Active: grade 3	Assisted active: grade 2	Assisted active/passive: grade 1	Passive: level 0
Abductor 5th finger	With the forearm resting on the table, palm facing down, put a rubber band around the 2nd and 5th fingers at the proximal interphalangeal joint for resistance. The patient should move the 5th finger as far from the 4th finger as possible. Hold for 10 s and return to the adduction position (Fig. 73.21)	With the forearm resting on the table, palm facing down, move the 5th finger as far away from the 4th finger as possible. Hold for 10 s and return to the adduction position	With the forearm resting on the table, palm facing down, move the 5th finger as far away from the 4th finger as possible. Using the other hand, the patient should complete the movement. Hold for 10 s or as long as they can and return to the adduction position	With the forearm resting on the table and the palm facing down, the patient should contract the abductor muscle of the 5th finger and with the help of the other hand, move the finger to its full range of motion, hold for 10 s and return to the adduction position	With the forearm resting on the table and the palm facing down, the patient, with the help of the other hand, should hold the abduction of the 5th finger in its full amplitude. Hold for 10 s and return it to the adduction position
Pollicis brevis	Forearm and hand resting on the table, facing up, put an elastic band of approximately 5 cm around the proximal phalanx of the thumb and forefinger forming a figure of eight. The aim is to raise the thumb perpendicular to the palm. Forming a 90° angle, hold for 10 s and return to the adduction position (Fig. 73.22)	Forearm and hand resting on the table facing up. Oppose the thumb to the other fingers to its full range of motion. Maintain the interphalangeal joint of the thumb in extension. The angle formed is 90° to the hand plane. Hold for 10 s and return to the starting position	Forearm and hand resting on the table facing up to oppose the thumb to the other fingers forming an angle of 90°.Use the other hand to complete the full range of motion, maintaining the thumb in this position and the interphalangeal joint in extension. Hold for 10 s and return to the starting position	With the forearm resting on the table and the palm facing up, the patient should contract the pollicis brevis. With the other hand move to the full range of motion. Hold for 10 s and return to the starting position	With the forearm resting on the table and the palm facing up, the patient, with the help of the other hand, should abduct the thumb to its full range of motion. Move the thumb in the perpendicular plane. Hold for 10 s and return to the starting position
Wrist extensors	Forearm resting on the table, palm down, hold an object with the maximum weight possible and lift the wrist. Hold for 10 s and return to the starting position (Fig. 73.23)	Forearm resting on the table, palm down, fingers semi-flexed, the patient should extend the wrist to its full range of motion. Hold for 10 s and return to starting position	With the forearm resting on the table, palm down and fingers semi-flexed, the patient should extend the wrist, as far as possible, completing the movement with the help of the other hand. Hold for 10 s and return to the starting position	With the forearm resting on the table and the palm facing down, the patient should contract the wrist extensors. With the other hand, move the wrist to its full range of motion. Hold for 10 s and return to the starting position	With the forearm resting on the table and the palm facing down, the patient should with the help of the other hand, extend the wrist to its full range of motion. Hold for 10 s and return to the starting position

Table 73.9 (continued)

Muscles	Resisted: grade 4	Active: grade 3	Assisted active: grade 2	Assisted active/ passive: grade 1	Passive: level 0
Extensor hallucis	Sitting with the leg supported on a chair, ask the patient to extend the hallux as far as possible applying counter resistance to the dorsum of the proximal phalanx of that toe. The resistance may be with the patient's own hand or using an elastic band. Hold for 10 s and return to the starting position (Fig. 73.24)	Sitting with the leg supported on a chair, to ask the patient to extend the hallux to its full range while keeping the other toes relaxed. Hold for 10 s and return to the starting position	Sitting with the leg supported on a bench or with the legs crossed to facilitate assisted movement, ask the patient to extend the hallux as far as possible. Assist the movement with the hand. Hold for 10 s and return to the starting position	Sitting with the leg supported on a bench or with the legs crossed to facilitate assisted movement, ask the patient to contract the extensor hallucis. With the help of the hand, move the hallux to its full extent. Hold for 10 s and return to the starting position	Sitting with the leg supported on a bench or with the legs crossed to facilitate assisted movement, the patient should with the help of the hand, extend the hallux to its full range of motion. Hold for 10 s and return to the starting position
Tibialis anterior muscle	Sitting with the leg supported on a chair the patient should perform dorsiflexion with a resistance on the back of the foot. This resistance may be by using an elastic band or bag around the dorsum of the foot. Hold for 10 s and return to starting position (Fig. 73.25)	Sitting with the leg supported on a chair the patient should perform dorsiflexion of the foot to its full extent. Hold for 10 s and return to the starting position	Sitting with the leg supported on a bench or with the legs crossed to facilitate assisted movement, ask the patient to perform dorsiflexion as far as possible. With the help of hand, complete the range of motion. Hold for 10 s and return to the starting position	Sitting with the leg supported on a bench or with the legs crossed to facilitate assisted movement, ask the patient to contract the tibialis anterior muscle. With the help of hand, make full dorsiflexion. Hold for 10 s and return to the starting position	Sitting with the leg supported on a bench or with the legs crossed to facilitate assisted movement, the patient should perform with the help of the hand, full dorsiflexion. Hold for 10 s and return to the starting position

important resources attempt to improve the quality of life, interpersonal relationships, and the exchange of experiences in the social context. During consultations, problems, doubts, and the difficulties encountered in the implementation of care are discussed with the patient in an attempt to find the best solutions, always observing the feasibility of changes and patients' willpower to change their habits.

These experiences can occur individually or in groups with the participation of a multi-disciplinary team trying to develop risk awareness, change attitudes, and increase autonomy.

Interventions can occur weekly or biweekly according to the availability of individuals and professionals.

Assessments and Measures for Surgical Rehabilitation

Reconstructive Surgeries

As a result of nerve damage, surgical rehabilitation aims to rebalance the action of deforming forces between agonists and antagonists to

Fig. 73.21 Resistance active exercise for the abductor muscle of the fifth finger

Fig. 73.22 Resistance active exercise for the abductor pollicis brevis muscle

Fig. 73.23 Resistance active exercise for the extensor muscles of the wrist

minimize disabilities and improve the function of the eyes, hands, and feet. The most common surgeries are correction of lagophthalmos, neural decompression, and tendon transfer to correct claw hand, opposition of the thumb, claw toes, foot drop, and varus foot.

Reconstructive surgeries of the arm are often performed to recover the intrinsic hand position and abduction and opposition of the thumb.

In the first case the muscle most commonly used as the motor is the superficial flexor of the third finger, which upon removal from the palm is split into four slips. The Zancolli technique is indicated in cases of hypermobile hands where each of these slips is sutured over the A1 pulley of each finger, forming a loop. However, the Brand–Bunnell technique is indicated when the hand is rigid. In this case the four slips are inserted in the back of the fingers at the so-called tendon assembly. The superficial flexor of the fourth finger is used with the Brand–Bunnell technique in the second case for abduction and opposition of the thumb. This tendon is exteriorized on the forearm and tunneled through Guyon's canal to

Fig. 73.24 Resistance active exercise for extensor hallucis muscle

Fig. 73.25 Resistance active exercise for the tibialis anterior muscle

the first metacarpal, where it is again exteriorized divided into two slips and sutured on the back of the thumb to the dorsal extensor tendon and the adductor tendon on the radial edge of the thumb [37, 38]. After correcting claw hand, use a circular plaster cast to position the wrist at 20° flexion, the metacarpophalangeal joints at 90° flexion, and interphalangeal joints at 0° flexion–extension

Fig. 73.26 Lengthening of the flexor tendons

(Fig. 73.39). To correct the loss of opposition of the thumb, the wrist should be placed at 20° flexion and the thumb in abduction and opposition.
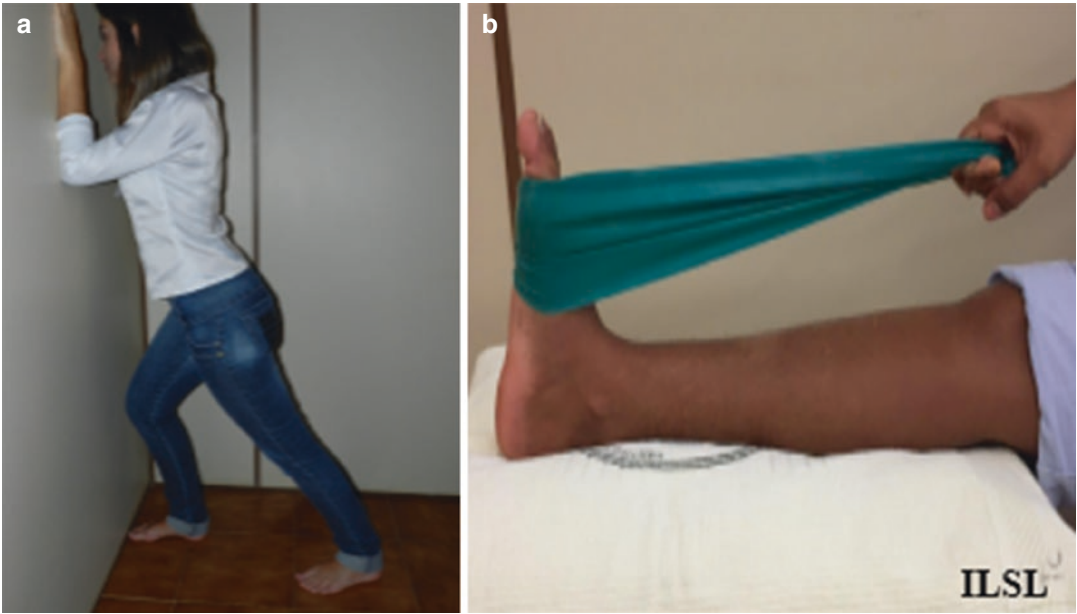
Fig. 73.27 (**a**, **b**) Lengthening of the gastrocnemius and soleus–calcaneal tendons

Fig. 73.28 Static orthosis with lumbrical bar for fourth and fifth fingers

Fig. 73.29 Static orthosis for night use

Reconstructive surgeries of the lower limbs are often performed to correct claw toes and foot drop. Normally the long flexor muscle of the toes is transferred to the extensors to correct claw toes. The tendon of the long flexor muscle of each toe is inserted into the extensor tendon at the proximal phalanx. The foot is immobilized using a plaster boot with heel for 6 weeks (Fig. 73.40). In the case of foot drop when the common pero-

Fig. 73.30 Orthosis to reduce retraction of the first intermetacarpal space and position the thumb in palmar abduction and opposition

Fig. 73.31 Serial orthosis to stretch the flexor muscles of the fingers

Fig. 73.32 Orthosis to reduce shortening of periarticular structures

Fig. 73.33 Serial orthoses to stretch the flexor muscles of the foot

Fig. 73.34 Harris splint

Fig. 73.35 Adaptations of household utensils to facilitate holding

neal nerve injury is complete, the posterior tibial muscle is divided into two slips and transferred to the dorsum of the foot where it is inserted into the extensor hallucis longus and extensor digitorum longus tendons. When the nerve injury is incomplete in foot drop, the tendon of the peroneus longus muscle is transferred to the dorsum of the foot and inserted on the side edge of the intertarsal ligament or the intermediate or lateral cuneiform [37, 38]. The foot is immobilized using a plaster boot without heel, with the ankle at 20–25° of dorsiflexion.

To obtain satisfactory results there are certain conditions that must be present preoperatively, such as:

Fig. 73.36 Thermal glove to protect from excessive heat

Fig. 73.37 Cloth to facilitate the use of soap
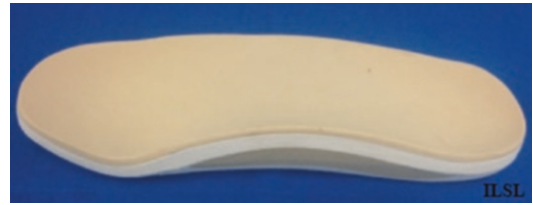
Fig. 73.38 Adapted in soles to improve plantar pressure distribution

Fig. 73.39 Plaster cast: wrist at 20° flexion, metacarpophalangeal joints at 90° flexion, and interphalangeal joints at 0° flexion–extension

- Completion of MDT for leprosy
- Be without leprosy reactions for more than 1 year
- Not have ulcers
- Have normal or close to normal muscle strength so that the transferred muscle can act properly in its new role
- Have functional passive joint mobility
- Capacity for contraction and individualized movement of the muscle being transferred
- Incorporate self-care practices

The objectives and conduct of the preoperative treatment [16, 38] are shown in Tables 73.10, 73.11, 73.12, and 73.13.

It is recommended to perform sensory, motor, and goniometric assessments, apply the Disabilities of Arm, Shoulder and Hand (DASH),

Fig. 73.40 Plaster cast with heel–ankle at 20–25° of dorsiflexion

Table 73.10 Objectives and preoperative rehabilitation conducts in tendon transfers

Objectives	Conducts
Maintain or restore the integrity and elasticity of the skin	Moisturize, lubricate and massage the skin (see Table 73.8)
Maintain or improve range of passive joint motion	Stretch muscle-tendon units of the hand/foot and first intermetacarpal space
	Perform passive exercises to stretch the tissue around joints
	Make static and progressively static orthoses
Isolate the muscle to be transferred	Active exercises to obtain individualized movement of the muscle to be transferred (Figs. 73.41 and 73.42). Avoid compensatory movements of the flexor and extensor muscles
Improve muscle strength	Perform exercises to strengthen the paretic muscles, especially the muscles that will function as the main motor after transfer
	Perform active resisted exercises to increase the muscle to be transferred (Fig. 73.43)

Fig. 73.41 Exercises to obtain isolated action of the superficial flexor muscle of the third finger

Fig. 73.42 Exercises to obtain isolated action of the posterior tibialis muscle

the SALSA scale, and the visual analog pain scale before and after surgery. In the case of tendon transfer in the hand, all the assessments above are applied with the exception of the DASH; however, the Jebsen–Taylor Hand Function Test should be added. The types of grip and support areas are also considered relevant to qualitatively assess the distribution of power and new patterns of grip acquired after surgery.

After surgery it is necessary to establish a motor rehabilitation program to regain motor control, aiming to recover the functional use of

Fig. 73.43 Resistance exercises to increase the muscle to be transferred

Table 73.11 Postoperative rehabilitation in the treatment of lagophthalmus

Week	Postoperative conduct
1, 2 and 3	Avoid stretching the temporal fascia
	Control edema
4 and 5	Start the functional rehabilitation program
	Recover the strength of the temporalis muscle
	Stimulate the correct use of transfer (achieve eyelid closure by bringing the dental arches together)

the hand for activities of everyday life and the foot during gait.

To guarantee a functional outcome after transfer, it is essential to correctly activate the transferred muscles, and automate and integrate the new movement pattern until there is an engram in the motor cortex. Otherwise the patient will revert back to the old pattern while using the hands or walking.

The activities proposed in the postoperative period are selected and conducted for the transferred motor unit, but always respecting the healing phases of the transferred tendon [16, 37].

More detailed information about the procedures before and after surgery for transferring tendons in the hands and feet can be found in the Manual of Rehabilitation and Surgery in Leprosy [37].

Table 73.12 Postoperative rehabilitation of the hand after correction of claw fingers and opposition of the thumb

Week	Postoperative conduct
1–3	Immobilize the operated limb (plaster cast)
	Position the arm in a sling
	Mobilize the adjacent limbs
4	Remove surgical plaster cast
	Make an orthosis with wrist at 20° flexion and hand in an intrinsic position (Fig. 73.44)
	Skin care
	Minimize edema (lymph drainage, compression garment, etc.)
	Avoid stretching the transferred unit
	Prevent or reduce adhesions of the skin, subcutaneous tissue and tendons
	Controlled passive mobilization of the first intermetacarpal space, and metacarpophalangeal and interphalangeal joints individually and collectively extension and flexion
	Complete passive mobilization is contraindicated after the Bunnell–Brand technique due to the insertion in the extensor apparatus
	Active assisted exercises to activate the transferred muscle: reeducate the new movement pattern (intrinsic position and opposition of the thumb) (Figs. 73.45 and 73.46)
	Maintain the use of daytime and nighttime orthoses
5	Maintain the items described above, as necessary
	Maintain or increase the range of motion of fingers and wrist
	Active exercises to activate the transferred muscle: reeducate the new movement pattern (intrinsic position and opposition of the thumb), and gradually increase muscle strength (Figs. 73.47 and 73.48)
	From the intrinsic position, gradually start active flexion exercises of the fingers
6	Maintain the items described above, as necessary
	Use only nighttime orthosis
	Goniometric evaluation to ascertain retractions, if necessary use orthosis

Table 73.12 (continued)

Week	Postoperative conduct
7 and 8	Maintain the items described above, as necessary
	Recover the motor control in activities requiring strength using the transferred muscle correctly
	Develop motor skills in daily activities such as putting on clothes, eating, hygiene, and writing (Fig. 73.49)
	Suspend the use of nighttime orthosis in the 7th week
	Encourage carrying out daily activities to automate the transfer
	Wrist range of motion to its fullest extent with the fingers relaxed

Neural Decompression

Neural decompression can be performed in the acute or chronic phase of the inflammatory process. When performed in the acute phase, there is a reduction in the constrictive action of the nerve, decreasing the intraneural pressure. With decreased pressure, an improvement in vascularization is expected with varying degrees of recovery of the motor and sensory functions and pain relief. In the chronic phase after more than 1 year of injury, surgery significantly reduces pain symptoms, although the consensus is that there is no recovery of motor or sensory functions [39].

After surgery without nerve transposition, the arm and forearm can be immobilized using a sling for a week and the leg immobilized using a leg orthosis for 2 weeks. When the ulnar nerve is transposed, the sling is associated with the use of an axillopalmar orthosis for 2 weeks (Fig. 73.50).

The main complaints in the postoperative period are inflammation, pain, swelling, and muscle spasms. The conduct will be established gradually during the healing process, ranging from mobilization of adjacent structures, scar massage, and gentle joint and neural mobilization.

The return to daily activities should take place progressively after 4 weeks.

Fig. 73.44 Orthosis with wrist flexion of 20° and hand in intrinsic position

Fig. 73.45 Enable
transfer to obtain the
intrinsic position

Fig. 73.46 Enable transfer for opposition of the thumb

Fig. 73.47 Motor skill
training

Table 73.13 Postoperative rehabilitation after correction of foot drop

Week	Postoperative conduct
1–6	Immobilize the operated limb (plaster cast with heel)
	Mobilize the adjacent limbs
	Isometric exercises for the quadriceps
	Gait training with crutches (without putting weight on the operated foot) After 10 days put some weight on the operated leg
7	Remove plaster cast
	Make orthoses positioning the foot at a 20–25° angle of passive dorsiflexion (Fig. 73.49)
	Skin care
	Minimize edema (lymph drainage, compression garment, etc.)
	Avoid stretching the transferred unit. Do not perform goniometry of plantar flexion
	Passive dorsiflexion exercises of the ankle in a sitting or lying position
	Exercises to activate the transferred muscle remembering the isolation trained in the pre-op (Fig. 73.50)
	Gradually increase the muscle strength
	Isometric exercises for the quadriceps
	Maintain range of motion (avoid plantar flexion of the foot)
8	Maintain the items described above
	Avoid the pending position in the intervals between exercises
	Continue to use daytime and nighttime orthoses
9	Maintain the items described above
	Start gait rehabilitation using parallel bars
	Active dorsiflexion and plantar flexion exercises (lift the heel from the ground) in the sitting position
	Assess the need for insoles, adapted foot wear
10	Maintain the items described above as necessary
	Active dorsiflexion and plantar flexion exercises as necessary
	Stimulate gait training ensuring the automation of transfer out of the parallel bars

Fig. 73.48 Orthosis to position the foot at a 20–25° angle of passive dorsiflexion

Fig. 73.49 Enable transfer to obtain dorsiflexion of the foot

Fig. 73.50 Axillopalmar orthosis for transposition of the ulnar nerve

Future Perspectives

The reduction in the number of leprosy cases worldwide with the use of MDT is considerable, but curing the disease does not mean that disabilities are eliminated. Recent studies show that around 40% of patients have some type of deficiency. Early diagnosis is still the best strategy to avoid deformities; however, once the disease is in place, measures can only prevent further disabilities and rehabilitate patients.

Future perspectives for preventive actions are related to developing the professional's ability to assertively identify disabilities, and to perform further research seeking new technology and innovative rehabilitation practices.

Possibly the only way to achieve good results is through patients adopting changes in their activities of daily life.

Glossary

Bacilloscopy A complementary examination in the diagnosis of leprosy. It consists of an analysis by microscopy whereby *Mycobacterium leprae* are observed directly in smears of lymph and intradermal scrapings.

Corneal opacity The cornea has a white appearance throughout.

Disabilities Problems in the functions or body structure due to significant impairment or loss.

Ectropion A medical condition where the lower eyelid turns outward.

Engrams The neurologic organization of pre-programmed patterns of muscle activity. Once formed, the same pattern is produced every time the specific nerves are activated.

Entropion Inward folding of the eyelid, whereby in the eyelashes rub against the cornea.

Froment's sign A test used to evaluate paralysis of the ulnar nerve, specifically the action of the adductor muscle of the thumb. The test assesses whether the patient can pinch hold a sheet of paper by thumb adduction. Patients are considered Froment positive when they have sharp flexion of the distal phalanx of the thumb due to instability of the metacarpophalangeal joint.

Graphesthesia The individual's ability with closed eyes to recognize the writing of words or numbers on the skin.

Hypoesthesia Decreased sensitivity in a particular region of the body.

Infiltration Increased thickness and changed consistency of the skin with less evidence of skin creases. It consists in using an instrument specifically designed to apply one or two tactile stimuli using parallel metal points. The distance between the points varies from 2 to 20 mm.

Lagophthalmos Inability to close the eyelids.

Lepromas Prominent subcutaneous nodules resulting from an accumulation of Virchow cells.

Leprosy reactions Acute and subacute inflammatory episodes that intermittently occur in

the chronic course of both paucibacillary and multibacillary disease.

Madarosis of the eyebrows Loss of hairs of the eyebrows.

Mycobacterium leprae Known as the cause of leprosy, this bacterium has a rod shape**.** It is alcohol acid-resistant and so staining during biopsy must be carried out using Ziehl–Neelsen stain.

Palpation Process of semiologic observation that consists in exploring a particular region of the body with the fingertips and palm.

Paresis Dysfunction of movement of one or more limbs.

Paresthesia Subjective sensations of the skin that can be described by the individual as cold, hot, tingling, pressure, among others. It may occur due to neural lesions, either by the destruction or by disruption of the nerve endings.

Proprioception A sense or perception of the movement of the body, balance etc. provided by the bones, muscles, tendons, and joints.

Skin ulcers (ulceration) The generic name given to any superficial lesion in skin tissue. A complication related to neuropathy in leprosy.

Stereognosis The ability to recognize objects by touch, shape, and contour.

Tinel's sign A test to check irritation of a nerve. A tingling sensation is felt in the distal end of a limb when an injured nerve is struck.

Trichiasis Eyelashes growing toward the eyeball.

Two-point discrimination test A functional test that evaluates the ability of the digits to act as a sensory organ. The test determines the minimum distance at which the patient is able to discern that two nearby objects touching the skin are truly two distinct points.

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Psychological Approaches in Treating Patients with Chronic Dermatoses

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Key Points

- Individual therapy: the treatment aims to work the patient's self-esteem and self-image, making effort to rescue their social, professional, and sexual interaction
- Family therapy: usually indicated for children and adolescents with psychodermatosis, the purpose is to share the responsibilities related to the presenting symptom and commit all members of the family to the treatment process
- Couple therapy: this therapeutic modality aims to share responsibilities about conflicts, even when symptoms are presented by only one partner
- Group therapy: this therapy assumes that participants have one common task and goal, and predicts a specific setting that meets the needs of space, frequency, and duration of meetings
- Psychodermatosis group with children: experience shows the importance of the participation of parents or substitute caregivers. For children, the group works as a setting to express feelings, anxieties, possible disabilities, and fears
- Psychodermatosis group with adults: the treatment aims to work with patients of both genders with different dermatologic diseases, more commonly psoriasis and vitiligo
- Psychoeducational group: group therapy for patients with atopic dermatitis: coordinated by a dermatologist and a psychologist, the group relies on the support of a multidisciplinary team, consisting of medicine, nutrition, psychology, nursing, and social work professionals.

Introduction

Cultural factors are known to influence directly the way each society expresses psychological distress. In diverse geographic locations and historical circumstances, feelings such as sadness, grief, and anxiety are represented differently, and may or may not be considered pathologic [1]. When treating the specific relationship between psychology and dermatology, it is necessary to underline one important element in our own popular culture that often leads us to associate what

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is on the "surface"—frivolity. When someone seems futile or simple-minded, for example, they are said to be "superficial." On the other hand, when a movie or work of art seems complex, interesting, and enigmatic, then we say it is "deep." In this sense, it is not unusual that patients presenting symptoms on the skin, the outermost and most superficial layer of the body, also underestimate the relationship that these pathologies have with "deep" issues in their lives, like the loss of loved ones, sudden changes in lifestyle, and other traumatic experiences.

The purpose of this chapter is to follow precisely the opposite direction, emphasizing the importance of the skin as a major somatic pathway of emotional expression, as well as to highlight the possible therapeutic approaches in Psychology. As the French poet Paul Valéry would say, "the most profound in the human being is the skin"; it is the organ that allows us tell the difference between the warmth of an embrace from the winter of solitude, the contours of happiness from the textures of sadness. The skin places us next to one another, approaches us to being human. Not accidentally, scars become symbols of one's life, and when important experiences do not leave physical marks spontaneously, they are translated on the skin through tattooed pictures or words. Our sufferings are no exception to this rule: their presence is expressed in paintings on this extensive screen called epidermis. The attempt to dispel the myth of "superficiality" related to skin symptoms and to provide a possibility to understand the existing intimacy between "skin labels" and "the deepest sufferings of the psyche" is common to all psychotherapy approaches related to dermatologic pathologies [2].

State of the Art

Psychology and Integrality

Dermatologic disorders are complex and multifaceted. They are usually related to emotional issues associated with important time periods in life, changes in family dynamics, or even trau-

matic past events. School issues, such as learning disabilities, and family matters, such as parental separation, may raise or exacerbate emotional disturbances. Adolescence is a time when one tends to leave the familiar context to experiment with new circles and is also one of the most vulnerable moments of the life cycle. The search for acceptance and other social demands that require maturity (still a developing issue for a teenager) are often associated with the high levels of anxiety and depression typical of this stage [3]. Maturity, in turn, is marked by several other emotional "challenges," such as building a career, getting married, and, later in time, the mourning process and the limitations of old age.

When such issues are addressed in public health services in Brazil, a country still frighteningly marked by social inequality and that only recently was consolidating its public policies, we must take into account the extreme influence that poverty, social vulnerability, and violence can have on health conditions, especially the mental health of individuals, families, and communities [4]. Racism [5], sexism [6], and homophobia [7], social forms of oppression quite widespread in Brazilian society, are factors that also influence considerably health conditions in women, afro-descendants, homosexuals, and transsexuals, and cause them to have problems accessing health services.

Therefore, to comprehend the various dimensions of a psychodermatosis, health services should offer, in addition to the medical view, the attention of a multidisciplinary team, capable of receiving and contextualizing people's distress in their social, affective, and family relations network. The more dynamic a team service is, the closer their different professionals work, the more comprehensive and complex will be the care provided by the health service. In collaboration, psychologists, social workers, medical doctors, nurses, nutritionists, and other health professionals will be able to understand the different dimensions of cutaneous disorders, taking into account physiologic, emotional, and social factors, and by doing so become able to indicate the best options for treatment [8] (Box 74.1). In addition, the principle of integrality in health care should be ensured, as it is proposed in the

constitution of the Sistema Único de Saúde (SUS), the Brazilian health care system [9]. From this broad and multidimensional understanding, it is possible to think of a singular therapeutic project (Box 74.2). In the case of children, for example, who often come to the service because of the issue of atopic dermatitis, the singular therapeutic project, from an Integrality perspective, would contemplate the possibility of interventions with families, social network, and, of course, the school, as will be discussed further.

Box 74.1 Integrality

Among the different meanings of this polysemic term, "comprehensive care" can be found, which means to understand the person who is a user of the health service network as a whole individual, considering biological, psychological, and sociocultural aspects [1].

Box 74.2 Singular Therapeutic Project

A comprehensive treatment plan that contemplates the possibility of medication prescription, psychotherapy, and interventions by the family of the patient in their territory and with other institutions [1].

Skin and Psyche Interface

As with most chronic diseases, many skin problems tend to affect and be affected by patients' emotional and family life. A study carried out in a dermatology outpatient unit, based on document analysis of 103 Psychological Screening Forms, found that stressors related to losses and separations in different stages of life were responsible for triggering and/or worsening psoriasis and vitiligo. Psychological effects of episodes of loss and separation have been studied by Bowlby since 1969, after what he called the Attachment Theory [10]. The author considers the establishment of bonds of affection and care as key issues for one's physical and psychological survival. These bonds are established in early childhood,

from the very care devoted to the baby by the mother or a substitute caregiver. When a child's emotional needs are appropriately met, there is a secure attachment. However, when the child is threatened or at risk and does not rely on protection and emotional support on the part of the caregiver, he/she may develop insecure or anxious attachment. According to Bowlby [11], this relationship pattern may extend into adulthood. These situations of loss or separation can cause stress in some individuals, and can trigger physical illnesses such as psychodermatoses.

Some psychological interventions have been assessed considering their impact on the improvement of symptoms of psoriasis. A cognitive behavioral program of symptom management showed benefits in the frequency and severity of symptoms, the strength of belief in the severity of consequences of the illness, and patients' attributions to emotional causes of their psoriasis. The authors compared the group that participated in the program with a control group after 6 months of intervention [12]. Another group of researchers [13] evaluated a single educational intervention also focused on patients with psoriasis. Information on disease and treatment was given. A high level of satisfaction with the intervention, improvement in knowledge about the disease, and better attitude toward therapy was reported even after 6 months.

In our outpatient unit, patients with psychodermatosis are seen by the Psychology service in a host session. From this first contact, they are referred to the therapeutic modality that both the multidisciplinary team and the patient consider more appropriate. Individual therapy, family therapy, couple therapy, and group therapy are among the possibilities of psychotherapy. In the following section, clinical case samples are presented to illustrate each of these therapeutic modalities.

Therapeutic Modalities

Individual Therapy

Psychotherapy may be indicated when the person is unable to solve a psychological conflict.

The therapist, then, works as a facilitator of a process of change, enabling the patient to build new insights about him- or herself [14]. Whenever a patient identifies psychological distress associated with the onset or worsening of skin disease, he/she may benefit from psychological assistance. This approach is especially used with adult patients and female adolescents, to address issues related to low self-esteem or body image distortions. Capisano [15] defines body image as "body's picture in the individual's mind." A result of anatomic, physiological, and sociological contributions, among others, and organized subconsciously, body image can go changing in accordance with our emotional manifestations. When the perception that one has of his body does not match the actual body, there is chance of deviations or distortions of body image. This is what usually happens to the person suffering from skin lesions. Skin diseases generally refer to the idea that the skin is ugly or "dirty" and that, therefore, the injury must be hidden. In severe cases, it drives the patient to social and sexual isolation [16]. It is important to identify which areas of the body are affected by dermatosis and try to relate episodes of stress that can be associated with the onset and/or aggravation of lesions. The treatment aims to work the patient's self-esteem and self-image, making and effort to rescue their social, professional, and sexual interaction.

Case Report 6.1
A 45-year-old man, who lives with his ex-wife and two teenage children. He came to psychotherapy because of his psoriasis, with lesions in arms and legs. His symptoms started 8 years ago, having been triggered after an accident in which he drowned and almost died. Then, he went bankrupt. During the meetings, the patient brought low self-esteem issues and difficulty expressing feelings. Facing family conflicts, expressing positive and negative feelings, especially with his mother, older brother, and children were the issues approached. He was a motivated patient

who had insight regarding his family history and his relationship patterns. At the end of 4 months, his lesions had virtually disappeared. He was instructed to return in the case of new significant stress with recurrence of skin symptoms.

Family Therapy

Usually indicated in pediatric and adolescent psychodermatosis, Family Therapy assumes that the symptomatic patient or "identified patient" is merely the spokesperson of some family dysfunction, and its treatment strategy is to investigate the affective and emotional relationship in at least three generations [17]. The purpose of therapy is to share the responsibilities related to the presenting symptom and commit all members of the family to the treatment process [18]. Intervention can alternate sessions with the whole family group (system), with individual sessions or subgroups: siblings, parents, female members, etc. (subsystems). Minuchin, Nichols, and Lee [19] defended the need for a collaborative approach of the therapist: the changes should take place within the limits and possibilities of each family group.

Case Report 6.2
An 8-year-old girl, with learning difficulties and obesity disorder. She was brought by her mother to psychological care under the guidance of a dermatologist who treated her *alopecia*. The girl had been gradually losing her hair since her parents' separation, which occurred 2 years before. After the separation, mother and daughter moved to the house of the maternal grandparents. The father brought his new female partner and her 8-year-old child to live in the former family home. With the news of her stepmother's pregnancy, her alopecia intensified. She came to the first appointment completely hairless, wearing a cap to hide her head. The family showed good

adherence to treatment, and followed all clinical and psychological recommendations. Family therapy consisted of alternating sessions with the girl and her mother, and with her father. Respecting the approach of the Singular Therapeutic Project, her teacher was included in the consultations, and there was a visit to the school for guidance for peers and teachers. The girl was revealing progress on school activities, could join a nutritional education program, lost weight, and improved her self-esteem. The family provided a natural hair wig, which negated the use of a hat. Despite all the efforts, the original symptom (alopecia), however, did not disappear. The benefit of treatment was to support the family, especially the mother, who came to accept her daughter's symptoms.

Couple Therapy

When dermatosis in an adult patient causes evident worsening in the couple's emotional and sexual relationship, the partner may be invited to participate in the therapeutic process. Couple therapy, as well as family therapy, does not imply that both partners are present in all meetings; couple meetings may be alternated with individual meetings with each one, but the emphasis of treatment is on the relationship [19]. This therapeutic modality aims to share responsibilities about conflicts, even when symptoms are presented by only one partner. It demands a collaborative, empathic, and committed attitude of the couple, with each other, and of the couple with the therapist.

Case Report 6.3
Male, 65 years old, presented symptoms of psoriasis and vitiligo, and sought psychological assistance due to marital issues especially on showing his lesions to his wife. Psoriasis-related lesions were more intense in legs and arms; vitiligo manifested on genitals exclusively. The patient reported a good social relationship of the couple. They used to travel a lot, have fun together, worked in the same place, and his wife was his boss. When asked about sexuality, he became surprised to realize it had been 6 years since they had their last sexual intercourse, precisely the time of appearance of the first lesions. The wife's presence was required and couple therapy recommended. Concomitant to clinical dermatologic assistance, couple therapy had to focus on issues of hierarchy, respect, and sexuality. The couple had good adherence to therapy, worked on the relationship, and recovered their sexual life. Lesions disappeared in a few months.

Group Therapy

Group therapy assumes that participants have one common task and goal, and predicts a specific setting that meets the needs of space, frequency, and duration of meetings. Although every group should respect the diversity of its members, it may be composed by age, gender, or symptoms of participants [20]. An intense therapeutic process, with affections, projections, and anxieties of so many people usually requires two therapists working together.

Psychodermatosis Group with Children

One possible approach for dermatologic manifestations in childhood is therapeutic groups with children and their caregivers. Experience shows the importance of the participation of parents in these groups, allowing separate spaces for working with children and also with their parents or substitute caregivers. For children, the group works as a setting to express feelings, anxieties, possible disabilities, and fears. Communication between therapist and children occurs by means of toys, play, and body language. It is all about creating a setting that makes it easier for children to access and communicate emotional issues using their playful world. For parents, it is to offer support in dealing with

children's skin problems, understanding them as issues for the whole family, and attempting to provide an environment for help and expression of feelings and doubts.

At our outpatient unit, this intervention is offered in a 12-weekly-meeting program, whereby a therapist is responsible for the group with children and other therapist is responsible for the group of parents or caregivers. Other health professionals may be invited to participate in the adult group as needed. Families come to these groups after a previous contact and evaluation in the Psychology Service. This contact helps to assess families' motivations, the desire and openness to group work, and the availability of participation in a weekly fixed schedule; both child and adult caregiver need to commit to the intervention. The program may be extended into family therapy modality whenever necessary.

Groups always happen simultaneously to medical treatment, never replacing it. They are valuable for skin improvement because they help families to gain insights into the problem, reduce the level of stress and anxiety, support and extend the adherence to medical treatment, and, in many cases, enable the identification and management of psychodermatosis-triggering situations.

Case Report 6.4
A boy, 7 years old, living with his father and mother. He had vitiligo all over the body, with onset of the disease a year later, when the family was evicted from the house where they lived. His father was an alcoholic. In group meetings, the boy looked introverted and lonely at first. Gradually he started to play and showed intense fear of losing his mother, as well as his sadness for having lost the house. At the same time, in the parents' group, father and mother could write their own story and also told the story of their children. The patient's mother said that he was her fourth child. The first pregnancy was a miscarriage. The second baby was raised by the paternal grandmother, after she and her partner separated.

The same happened with the third baby. Our patient was the first child raised by mother and she would not consider leaving him. She was experiencing serious marital problems, which led to the loss of the house, but custody of him was not an issue. His siblings' story was unspoken but seemed to be alive to him, and he was afraid of being abandoned too. After these feelings were identified, the theme was approached with mother and child, separately, in group sessions. The expression of fears, anxieties, and frustrations was encouraged, to relieve him and minimize the manifestation of skin symptoms. Mother-and-child group session followed; communication and affection were stimulated. Gradually the symptoms of our patient decreased until they became almost unnoticeable.

Psychodermatosis Group with Adults

Groups with adults welcome people of both genders with different dermatologic diseases, more commonly psoriasis and vitiligo. Usually they are arranged according to age (20–40 years, for example) and psychological characteristics of patients. People with alcohol issues or other drug use or people with psychiatric commitment do not usually benefit from this approach. Intervention occurs weekly, lasting 1 h and 30 min for a period previously determined by the participants, usually 4 months. Coordination is typically performed by two therapists.

Case Report 6.5
Male, 36 years old, worked as a professional cleaner. Vitiligo on the face was very evident in his black skin. During a host interview in the Psychology service, he reported that the first episode of vitiligo occurred at age 6, after his mother's death. At that time, he responded well to dermatologic treatment. At 8 years of age, his teacher of the second grade died, victim of

a car accident. The lesions returned, weaker, and he resumed dermatologic treatment for another year. He had been clear of lesions since 9 years old, but had lost his wife 1 year later, victim of breast cancer. His only daughter, 16, became pregnant immediately after. His current vitiligo condition was the most severe he had ever had. He resumed, on his own, using the former medication, with no effect. His current dermatologist referred him to immediate psychological assistance. He started individual psychotherapy and then was invited to join a group of patients living with psychodermatosis. Group work had an emphasis on patients' self-care and recovery of self-esteem. He was welcomed by the group, had support in his grief process, and was oriented due to caring for his pregnant daughter. As therapeutic work strengthened him, and with his good adherence to dermatologic treatment, the lesions disappeared. He was discharged from therapy with fully repigmented face; he was happy to regain his black identity.

Psychoeducational Group: Group Therapy for Patients with Atopic Dermatitis

Ferreira et al. [21] studied the dynamics of relationships of families facing atopic dermatitis and found that the frequency and intensity of symptoms are influenced by stressors, especially those linked to episodes of loss and separation. Staab et al. [22] assessed contributions from groups with children and adolescents with atopic dermatitis and their parents in an outpatient hospital in Germany. They had 6-week meetings, comparing the group with standard intervention. Group participants had a 12-month follow up and were significantly better when compared with the control group as to the severity of eczema, subjective severity, and quality of life of parents of affected children younger than 13.

To meet a proposition of the AADA (Association for Support of Atopic Dermatitis in

Brazil), a group of patients and relatives living with this disease was created in the Ambulatório de Dermatologia Sanitária. This is an open psychoeducational group that gathered monthly on Saturday mornings for a nonstop period of 10 years. Coordinated by a dermatologist and a psychologist, the group counted on the support of a multidisciplinary team, consisting of medicine, nutrition, psychology, nursing, and social work professionals.

Group dynamics included three distinct stages: firstly, family members and patients were welcomed by the multidisciplinary team in a large auditorium. Presentations were made and general guidance on dermatosis was given. In a second stage, family members remained in the room while children and adolescents were moved to another room. At each meeting a common theme was proposed for discussion, including recreational resources for the children. Themes complied with participants' request, generally associated with care in different seasons of the year (e.g., attention to swimming pools and sun exposure in summer; hydration and use of cotton clothing in winter) or a related date (attention to diet at Easter, for example). At the end of the activities, children and family gathered one more time to exchange experiences. The group finished with a healthy snack, proposed by the nutritionist in the team [23].

Case Report 6.6

Girl, 6 years-old, participated in the Atopic Dermatitis Group for 2 years, always accompanied by her mother. She was an only child, both parents were health professionals; her mother had left the job to devote herself to the girl's care, who had been suffering severe attacks of atopic dermatitis since the age of 2. Alice had lesions all over her body and cried a lot when showering, scratched herself at night, and only accepted her mother to treat the injuries, although her father was a professional nurse and was willing to help. Initially, the girl remained absolutely silent during group sessions.

In the children group she was always alert, performed the activities proposed, but interacted little. She never talked. During the treatment, she would gradually become more participative. The girl enjoyed graphic and music activities, especially when one of therapists played the guitar to the group. The lesions that marked her face were decreasing. At school she became more independent, and even participated in the dance group. Her mother was supported in order to share the child's care with her father. The girl participated in the groups for 2 years, being discharged with great deal of autonomous care. The mother began to devote herself to other activities, and considered going back to work.

Perspectives and Final Considerations

An integral service of dermatology must offer a number of psychotherapeutic possibilities for the treatment of psychodermatosis. The wider range of treatments allows one to respond uniquely to each new case referred. The choice of an individual, family, or group approach should be made, however, only after a first contact of general acceptance and multidisciplinary assessment. Psychotherapy, regardless of the modality, reaches only one of the dimensions of an illness and can only be really effective if it is in tune with medical, nursing, nutritional, and social care.

Understanding that the "skin" communicates something with its symptom is of key importance in the psychological care of psychodermatosis. As Campos [24] says, "Body language is the first, the most primitive means of communication and defense of a human being. It is natural, therefore, to continue to use it throughout life, especially at times when other forms of communication and defense are locked (or have not been learned)." In this sense, a psychologist's first task is to help in a translation process: to help the patient to express in words the emotions, feelings, and distress that have been overloading their body so far.

Psychotherapy is not always able to provide a complete remission of skin symptoms. Sometimes it is all about changing the *relationship* the patient has with his symptoms, or the family's relationship with the patient, so that symptoms stop producing so much pain and can be given new meanings, subjectively [25]. One of the patients in the clinic, Ingrid, 16, illustrates how the process works. She says, "... broke up with my first boyfriend, began to work and help mother, and the stains increased. From then on, every speck (vitiligo) symbolizes a different problem. But I do not need stains to keep my problems. I have no reason to keep them because others will come. (Ingrid, 16 years old)".

Scars are permanent, but may no longer be horrific memories and become symbols of bravery. Skin stains, similarly, may be indelible; but to stop being just symptoms of a disease they can count on the help of psychotherapy.

Glossary

Multidisciplinary approach In collaboration, psychologists, social workers, medical doctors, nurses, nutritionists, and other health professionals will be able to understand the different dimensions of skin-related pathologies to indicate the best options for treatment.

Psychodermatoses Multifactorial dermatoses whose course is subject to emotional influence.

Psychological interventions Individual therapy, family therapy, couple and group therapy are among the possibilities of psychotherapy presented, besides psychoeducative interventions.

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